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DEPARTMENT OF HEALTH FOR SCOTLAND

DIPHTHERIA

Report by the Infectious Diseases Sub-Committee
of the Scientific Advisory Committee

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FOREWORD

Diphtheria is a disease of primary importance in British epidemiology. A wave of high incidence passed over the country, reaching its peak some eight years ago. At that time, in 1940, the Sub-Committee on Infectious Diseases Research of the Scientific Advisory Committee recommended that diphtheria immunisation should be applied as a national measure in Scotland. Since then the Sub-Committee have maintained their interest in this technique of preventive medicine.

The Sub-Committee considered a detailed field survey of the disease over a long period—a project originally suggested by Dr J. Ritchie, who was then one of its members—but, because of staff shortage, they decided to limit their inquiry to a specific question. This question was precisely how, admitting that inoculation does not always prevent the occurrence of clinical diphtheria, does inoculation modify the disease?

The Report contains the results of the investigation of the members of the Sub-Committee working as a team; its contents will, I am sure, be of interest and value to workers in many countries. At this time, when many countries have populations partly or largely inoculated, we must expect modified cases of diphtheria to form a large proportion of hospital admissions. Thus, a feature of the Report is its study of the changing character of diphtheria as manifested in a large section of the population of Scotland.

It is right to add that the Report owes much to the skilful planning of the inquiry and the assembly of the relevant material by the Medical Secretary.

A.S.M. Macgregor

Chairman,
Scientific Advisory Committee.

St Andrew's House,
Edinburgh.
October, 1948.

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A Comparison of Diphtheria in Inoculated and Uninoculated Persons in a Partly Inoculated Population

The main results of diphtheria immunisation have been described in statements issued from time to time by the Ministry of Health and the Department of Health for Scotland, and can be compressed into the broad statements that inoculated persons acquire clinical diphtheria less frequently and very rarely die of the disease. There is, however, relatively little evidence of the comparative characteristics of diphtheria in the inoculated person, contrasted with the uninoculated person in similar environment and at the same time. It therefore seemed that an inquiry into these differences—accepting their existence—would be of interest. The results of such an inquiry will be described in some detail in this report.

All patients admitted to certain Infectious Diseases hospitals in Scotland in the calendar year 1942, and accepted as suffering from diphtheria, had their histories summarised on an agreed card, the data so collected being coded and entered on 36-column punched cards for analysis.

A copy of the card used by the different centres is printed as Appendix I to this report. The details of this card need no explanation except that the front of the card has one heading "Approximate Date of Immunisation" and that space is provided for fuller and more precise information on the back. This arrangement was devised because medical officers of hospitals could not always obtain detailed immunisation histories, and such partly completed cards were then referred to the Medical Officer of Health for completion. The card was devised to conform as nearly as possible to an existing form of recording in use in Glasgow.

The hospitals participating in the inquiry were as follows :—

Glasgow :	Belvidere, Knightswood, Ruchill and Shieldhall Hospitals (data obtained through the Medical Officer of Health).
Dundee :	King's Cross Hospital.
Aberdeen :	City Hospital ; Aboyne, Fraserburgh, Inverurie, Peterhead and Stonehaven I.D. Hospitals. Dufftown, Eastbank, Elgin, Gilbert Bain and Tingwall Hospitals (data obtained through the Medical Officers of Health).
Lanarkshire :	County Hospital, Motherwell.

An inquiry such as that outlined was bound to yield information on issues other than those to which primary attention was devoted. Indeed, on a survey of the results, it has been considered that some of the information on the general characteristics of the disease may transcend in interest the findings in regard to the original intention of comparing its manifestations in inoculated and uninoculated patients (and in particular, on the attempt to find why the disease is so much less fatal to the inoculated). As a result, the following report is presented in two parts. The first describes the natural behaviour of diphtheria in the period and places under review : the comparison of the inoculated and uninoculated forms the second part.

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PART I

1. The constitution of the population surveyed

A total of 4,272 patients had their records summarised and included in the inquiry. In Scotland in 1942, 9,340 patients were admitted to hospital suffering from diphtheria. The study population, therefore, forms 45·7 per cent. of the hospitalised diphtheria cases in the year. The city part of the patients included in the inquiry was 3,794, or 60·1 per cent. of the 6,316 diphtheria cases removed to hospital in large burghs in Scotland during that year. No doubt this latter figure included some patients whose homes were outside the cities, though treated in city hospitals. The remaining 478 patients represented only 15·8 per cent. of the 3,024 cases removed to hospital in Counties in Scotland. We present these percentages with some reserve, but there is no doubt that the study sample was biassed towards a selection of city cases as opposed to cases in other large burghs and counties.

2. Sex and Age

So far as sex solely is concerned, three main observations may be made. First, Appendix Table I shows that the sex ratio is uneven, for 58·5 per cent. of the total are females. This is in accordance with the known distribution. Study of this uneven sex distribution led to a closer survey of the age distribution in the two sexes which will be dealt with further in the next paragraph. It was found, however, that the excess of females at all ages was due to an excess at only those ages over six years. Differentiation of Scottish notifications by sex is not, unfortunately, available for the 1942 figures.

Some tabular data prepared by the Department of Health for Scotland are shown below :—

TABLE A

Age Group	Scotland, 1944–46 : Diphtheria Notifications		
	Males	Females	Per Cent. Males in Total
All Ages ...	7,040	9,396	42·8
0–1	150	114	56·8
1–4	2,039	1,940	51·2
5–14	3,523	4,255	45·3
15–24	804	1,734	31·7
25–34	320	826	27·9
35–44	138	318	30·3
45–64	53	196	21·3
65–	13	13	50.

The figures for 1944–46, tabulated above, show a sex trend with age very similar to that found in the patients included in this inquiry. It is considered that in this respect the sample in the inquiry must be regarded as satisfactory ; this trend towards an excess of female cases over the age of six is regarded as an interesting observation to which further reference is made.

In the second place, the fatality rates for males and females are 3·67 per cent. and 2·48 per cent. respectively. This difference, which is not great, is explained when the age distribution is again considered for there is an excess of females in the older age groups. Such an age distribution should produce a lower fatality rate. When the distributions of recoveries and deaths in the different age groups are compared, there is a significant excess of deaths in the younger age-groups of each sex and the fatality rates of both are similar, age for age. The apparent differences between the crude fatality rates in the sexes having been found to have no significance, sex was not an important factor in determining fatality at any given age.

The third observation is in regard to complications. It was found that, of the 1,773 male cases, 736 (41·5 per cent.) developed complications, whereas for 2,499 female cases, the figure was 1,010 (40·42 per cent.). It thus seems that the development of complications is, broadly, independent of sex. Such a statement, however, must be modified in detail to take account of the quite different age distributions of the two sexes. When compared by age groups the figures briefly tabulated below were obtained :—

TABLE B

Age Group	Males		Females	
	Total	With Complications	Total	With Complications
0–4	574	240 (41·8%)	571	277 (48·5%)
5–9	597	300 (50·2%)	679	298 (43·9%)
10–14	255	92 (36·1%)	368	129 (35·0%)
15–24	247	80 (32·4%)	579	202 (34·9%)
25–	100	24 (24%)	302	104 (34·4%)

The sex differences in complication incidence rates are significant at ages under 5 and 5–9 (though it should be noted that the excess is in *females* at the first age period and in *males* at the second) ; in other age groups the differences are insignificant. The distribution as a whole, however, (over all age groups) is not a chance one. While stating this fact, we have found indices of the state of the patient which we must regard as more important than sex and, in view of the need for limiting subdivision of tables, we decided not to classify further tables according to sex.

Age is of obvious importance in infectious diseases—not only because of its effect on fatality but because the age distribution of the cases may itself show unusual characters. In most of the Appendix tables, therefore, age has been included, even when its effect is not always apparent. A summary of the relevant portion of Appendix Table I supplies some interesting data.

TABLE C

Age Group	Males	Females	Totals*	Fatality Rate Per Cent.
0–4	574	571	1,145 (49·9%)	5·85
5–9	597	679	1,276 (53·2%)	2·51
10–14	255	368	623 (59·1%)	2·25
15–24	247	579	826 (70·1%)	0·97
25–	100	302	402 (75·1%)	1·49
All Ages ...	1,773	2,499	4,272 (58·5%)	2·97

* Per cent. Females in brackets.

We have already referred to the unequal distribution of the sexes by age-groups. The preponderance of female cases becomes most marked in those over the age of 15 years where almost three-quarters of the total cases are female.

That this is not a mere accident peculiar to the population under examination is shown by referring again to the figures for Scotland for 1944–46 which present a similar picture. At first sight this difference seemed surprising for it is given no prominence in recently published text books in Infectious Disease. Ker (1909) however, referred to the increased incidence in females over 10 years, and it is interesting to repeat his observation after a lapse of 33 years, especially when we consider the changes in social habits that have occurred in that time.

In considering possible reasons for such sex differences, we first reviewed a theory that the relative sparing of males might be due to an earlier acquisition of natural immunity. Such a process, however, would inevitably be accompanied by a relatively high incidence of diphtheria in males in those earlier years when the presumed immunity was being acquired. Of this, there is no evidence in the data. Indeed, it seems more likely that diphtheria should be regarded as very largely a household infection and we tend to ascribe the higher incidence in females over the age of 5 to their social habits which still involve a greater attachment to the home and to closer contact with children.

Reference to Table C also shows the well known association of age and fatality rate. The higher rate obtained in persons over 25 years of age may be explained by the fact that a number of patients in a general hospital ward outbreak was included; these patients suffered from other diseases which in themselves might have proved fatal. The over-all fatality rate of 2·97 per cent. is a low one, especially when it is considered that at the time of the survey (as will be pointed out later) *gravis* strains constituted the main infecting type. It may be noted that the fatality rate for Scotland in 1942 (3·06 per cent.) was the lowest observed in a series running from 1911 (McKinlay (1947)). The national figures show that, at the time of our survey, diphtheria in Scotland was declining in severity as assessed by fatality rate.

3. Complications

Of all patients, 1,746 (40·87 per cent.) were listed as developing some complication. The information recorded on the cards was subjected to analysis when it was found that the different complications covered a very wide range—many of them being little more than chance occurrences. Moreover, the very fact that the records were collected from a number of different centres, where different standards of diagnosis and recording prevailed, made us feel that no useful purpose would be served by recording our detailed analysis of the information. We have therefore concentrated our attention upon those toxic complications of diphtheria affecting the nervous and circulatory systems which one might expect to be uniformly reported by all centres.

TABLE D

Toxic and other Complications, by Result

Nature of Complications	Cases	Deaths	Fatality Rate
A. Nerve Paralyses[1]	155 (3·6%)	7	4·5%
B. Circulatory[1]	286 (6·7%)	63	22·0%
C. Nervous plus Circulatory[2] ...	36 (0·8%)	9	(25·0%)
D. Other Complications	1,269 (29·7%)	29	2·3%
E. None Recorded	2,526 (59·1%)	19	0·75%
All Cases	4,272 (100%)	127	2·97%

[1] Alone or in any combination, except for those in line C.

[2] Including any combinations with "Other Complications."

The figures contained in Table D have considerable interest for it is apparent that the incidence of toxic complications was not as high as might have been expected. The table also draws attention to the gravity which attaches to the development of circulatory complications in the course of diphtheria for it will be seen that over half of the deaths occurred in patients who had developed this group of complications. It seems to us likely that minor degrees of affection of the circulatory system might not be detected or recorded, so that the figure in the table presumably refers particularly to the severer forms of circulatory damage, the gravity of which is further reflected in the high fatality rate encountered.

As for nerve palsies, the incidence was not of itself high, and in this case we may reasonably assume that recording was fairly accurate for, with the exception of paralysis of accommodation which is probably often missed in the youngest age groups, such complications are likely to be clinically manifest. The development of a nerve paralysis alone was obviously not of serious prognostic significance, although the result was worse in cases with nerve palsies than in those without them. Their combination with a circulatory complication yielded (not unnaturally) a group with worse results than any other in the inquiry. In uncomplicated cases, the fatality rate was 0·75 per cent.

It has seemed valuable to analyse the occurrence of these complications in respect of the different age groups. Table E summarises the information which will be found in Appendix Table II.

TABLE E

Cases with Toxic Complications, by Age Groups

Age Group	Total Cases	Nerve Paralyses		Circulatory Complications		Combined Rates
		Cases	Incidence Rate	Cases	Incidence Rate	
0–4	1,145	47	4·1%	89	7·8%	11·9%
5–9	1,276	59	4·6%	115	9·0%	13·6%
10–14	623	13	2·1%	42	6·8%	8·9%
15–24	826	24	2·9%	27	3·3%	6·2%
25–	402	12	2·9%	13	3·2%	6·1%

From the table it is apparent that the incidence of these toxic complications is appreciably higher in those under the age of 10. When the two forms of complication are subdivided it is interesting to find that the higher incidence of circulatory complications, previously referred to, shows a definite association with age—because in those over 15 there is little difference between the incidences of nervous and circulatory complications. Put in another way, it may be that natural resistance is sufficient by age 10 to reduce the incidence of nervous complications but not sufficiently established for another 5 years to have the same effect upon the incidence of circulatory complications. The association of certain complications with the type of organism will be dealt with under the latter heading.

4. Seasonal Distribution

This distribution (Appendix Table III) shows little that needs special mention. The peak of incidence was in the fourth quarter of the calendar year, but the peak of fatality in the first quarter; the third quarter provided fewest cases, fewest deaths and the lowest fatality rate. Recorded complication incidence per quarter was (1st) 47·2 per cent., (2nd) 41·5 per cent., (3rd) 43·2 per cent. and (4th) 32·5 per cent. ; over the year it was 40·87 per cent. The low incidence in the fourth quarter will be noted, but the series covers too short a time to enable us to make a wider statement than that the observed distribution of complications, by seasons, could not reasonably be attributed to chance.

5. Days Ill prior to Admission

Study of the relationship between duration of illness on admission and the ultimate outcome shows the general trend which has so often been referred to in the past, i.e. that fatality rate rises with delay in admission. It is interesting to contrast this result in a toxic disease with that which we previously reported in the case of meningococcal meningitis (1944). It will be recalled that in the latter disease treated with sulphonamides there was no apparent relation between early admission and good results. It has, however, interested us to correlate the duration of illness on admission with age, and the results are shown in full in Appendix Table IV from which we have abstracted the following summary table which is graphically shown in Appendix Chart 1.

TABLE F—See Appendix Chart 1

Proportional Distributions of Age Groups for each Day Ill on Admission

AGE GROUP	DAYS ILL ON ADMISSION						
	1	2	3	4	5	6–	Unstated
0–4	30·0%	24·8%	24·6%	26·2%	31·2%	29·6%	37·4%
5–9	32·8%	35·2%	28·9%	27·7%	22·9%	24·9%	23·2%
10–14	11·9%	16·8%	15·3%	13·6%	14·0%	12·2%	10·1%
15–24	19·0%	16·7%	20·9%	21·1%	21·2%	20·1%	14·1%
25–	6·2%	6·5%	10·3%	11·4%	10·6%	13·2%	15·2%
All Ages ...	100%	100%	100%	100%	100%	100%	100%

The chart shows (as does Table F) that, in the stated age groups, the largest number of admissions after one, two, three or four days' illness was of children aged 5–9, whereas the largest number admitted after longer illnesses was that of children under 5. It should be observed, however, that the smallest number of admissions after one to five days' illness (inclusive) was that of patients over 25, and that the smallest number with a longer duration was among patients aged 10–14. These differences could quite easily be explained, in those under 5 years, by the fact that the insidious onset of diphtheria in them results in little complaint and therefore in a later recourse to medical aid. In the older patients it would seem possible that the question of diphtheria is considered by the doctor only after a preliminary diagnosis of tonsillitis has been made, with a resulting later admission. This latter point is referred to again when the site of the lesion is discussed.

We have compared the distributions of duration of illness on admission in patients infected with the individual types of organism. The results are tabulated in Appendix Table V. For each type there is a nearly steady progression from low fatality rates, after early admission, to higher rates after later admission. We have also calculated the distributions of duration of illness on admission, within each type. The figure (Appendix Chart 2) shows that there is a slight tendency towards delay in admission of mitis cases ; there is very little difference between the distributions of gravis and intermedius, which cases tend to be admitted slightly earlier. Such a finding is in keeping with the more rapid development of symptoms when the infection is with these types. Untyped cases were, on the whole, admitted early and in particular in unduly large proportion after two days' illness.

6. Types

The number of cases in which type was recorded was 3,187, distributed in the following proportions :—

Gravis	2,219	(69·63 per cent.)
Intermedius	640	(20·08 ,, ,,)
Mitis	328	(10·29 ,, ,,)

Such a distribution conforms with that given by Carter (1944) for Glasgow in 1942. This preponderance of gravis infections in respect of the two purposes of this report is unfortunate. Not only is the total number of cases in each of the other types small, but the mortality produced by them is comparatively insignificant. The type with lowest fatality rate was intermedius, but in fact there was no significant difference between the rates in intermedius and in mitis infections. From this point of view, the inquiry might be said to include only two groups of infections—(*a*) gravis and (*b*) others.

Study of the age distribution of the three types (Appendix Table VI) shows that the distribution was very even. This finding is somewhat surprising in that bacteriological evidence would suggest that gravis was a comparative newcomer to Scotland, or at least had been little prevalent, some five years before (Carter). A somewhat older age distribution might therefore have been expected with this type. We must conclude that the resistance produced against the then prevalent types was protective even against the gravis type which is regarded as having more invasive capacity (McLeod *et al.* (1939)). Our figures cannot of course prove that changes in age distribution did not occur at a time when active changes were occurring in type prevalences.

The toxic complications associated with these three types are listed in Appendix Table II. If these are summed, the following complicated case rates (toxic complications only) are obtained :—

Gravis	13·1 per cent.
Intermedius	9·05 ,, ,,
Mitis	7·6 ,, ,,

This sequence differs from that of mortality, so we have examined the figures in more detail and have found that, the whole distribution not being attributable to chance, the only significant difference was between complications due to gravis and those due to other types. This confirms the distinction made in respect of mortality, i.e. that in the population studied the differences between intermedius and mitis were not of great magnitude.

It may be noted that a considerable proportion of the cases was untyped. For most of the age groups the proportion of these cases followed a pattern similar to that of the typed cases, but there was an exception in those under the age of 5 (Appendix Chart 3); here the proportion untyped was significantly high. Further study of the " unstated type " cases has shown that, in addition to their youth, significant differences from typed cases were earlier admission to hospital and a higher complication rate. In spite of these differences there was nothing else to indicate that the " unstated type " cases were inconsistent with typed cases in their general characteristics (including incidence of toxic complications), so that they have been regarded as acceptable in this review of cases of diphtheria. In so doing, it was borne in mind that, in some cases, diphtheria bacilli had been recovered but had not been typed.

7. Site

The classification of the local lesion was broadly that of the Superintendents' Committee of the L.C.C., the main distinction being between membrane confined to the tonsils and membrane extending beyond the tonsillar bed. Because of the small numbers of cases in certain classes, we have divided the data into three main groups, (*a*) tonsillar, (*b*) pharyngeal and multiple, and (*c*) others. In the majority of multiple site cases, the pharynx was in fact involved. The distribution of cases in these three groups was as follows :—

Tonsillar	3,169	(74·2 per cent.)
Pharyngeal and Multiple	544	(12·7 ,, ,,)
Others	559	(13·1 ,, ,,)

It seems to us that this distribution is much more uneven than would be expected, since it includes an undue proportion of Tonsillar cases. This might be related to the admission of most patients early in their disease for nearly 40 per cent. were admitted on or before the third day of illness. Even if this suggestion is not the explanation, it is important to realise that this high proportion of tonsillar infections is bound to reduce the severity and must be taken into account in considering the low fatality rate observed in our series. This point is further emphasised by Appendix Table VIII, which shows that less than 15 per cent. of the cases were classified as having severe toxæmia on admission to hospital.

The influence of site on fatality rate is shown in broad outline by the following figures :—

Tonsillar	1·20	per cent. fatality rate.
Pharyngeal and Multiple	13·42	,, ,, ,, ,,
Others	2·86	,, ,, ,, ,,

The distinctions between the various fatality rates by sites persist with little relative change when comparison is limited to particular age groups. In regard to the distribution of the different sites in age groups, the figures are shown in Appendix Table VII, from which the subjoined Table G has been compiled; the data are shown graphically in Appendix Chart 4.

TABLE G—See Appendix Chart 4

Proportional Distribution of Sites for each Age Group

Age Group	Sites			
	Tonsillar	Pharyngeal plus Multiple	All Others	All Sites
0–4	69·8%	12·2%	18·0%	100%
5–9	78·9%	11·4%	9·7%	100%
10–14	75·4%	10·9%	13·6%	100%
15–24	74·8%	14·9%	10·3%	100%
25–	68·4%	16·9%	14·7%	100%
All Ages ...	74·2%	12·7%	13·1%	100%

We should comment particularly on two figures—(*a*) the relatively high proportion of other sites at ages below 5 and (*b*) the relatively high proportion of Pharyngeal and Multiple in persons over 15. In explanation of the former it may be stated that the figures have been examined and it has been found that the excess is due to the inclusion in this class of the cases of anterior nasal and laryngeal diphtheria, which of course mainly affect the youngest age group. An explanation of the latter is not so easy, but it may be suggested that, in this age group, in the differential diagnosis between tonsillitis and diphtheria the practitioner might be inclined to favour tonsillitis ; and it may be recalled that in reviewing the duration of illness on admission, we noted a tendency towards later admission of patients in this age group.

Considering the site distribution by types, the following proportions are obtained :—

TABLE H

TYPE	TONSILLAR	PHARYNGEAL AND MULTIPLE	OTHER	ALL SITES
Gravis	71·1%	16·1%	12·8%	100%
Intermedius ...	74·7%	11·7%	13·6%	100%
Mitis	72·9%	6·1%	21·0%	100%

Perhaps the three most striking figures are first, the high proportion of "pharyngeal" in gravis infections ; second, the low incidence of "pharyngeal" in mitis ; and thirdly, the high proportion of "other sites" in mitis infections. The last point may be mentioned first for the explanation already given that "others" contain an undue proportion of laryngeal and nasal diphtheria, almost certainly accounts for the high figure obtained. In view of McLeod's suggestion that the mitis case usually exhibits more extensive membrane, our first two observations are puzzling and apparently not in conformity with his observations. It must be recalled that the very uneven distribution of the cases by types should occasion reserve in quoting proportions in the mitis groups, where some of the figures are small. In view of this, when we considered the question of mortality of the different types in different sites, we decided to combine Mitis and Intermedius figures with the following interesting result :—

TABLE J

SITES	GRAVIS		INTERMEDIUS AND MITIS		FATALITY RATES		RATIO OF RATES (A/B)
	Cases	Deaths	Cases	Deaths	Gravis (A)	Intermedius & Mitis (B)	
Tonsillar ...	1578	28	717	2	1·8%	0·28%	6·4 : 1
Pharyngeal and Multiple ...	357	59	95	7	16·6%	7·4%	2·2 : 1
Others	284	9	156	1	2·84%	0·64%	4·4 : 1

It is evident that the ratios of the fatality rates are far from uniform, for whereas gravis is six times more fatal than intermedius and mitis in tonsillar diphtheria, it is only twice as fatal in pharyngeal and multiple sites. The following reasoning may be applied in explanation of these differences. The form of attack by the gravis organism is such that when membrane is confined to the tonsils some factor so enhances toxæmia, that the fatality rate is excessive. Once membrane has extended beyond the tonsillar area, the form of toxic attack becomes less important and the lethality of the different strains becomes more approximately equal.

Summary of Part I

This review of 4,272 cases of diphtheria occurring in certain areas of Scotland in 1942 has shown the following features :—

1. The cases were of a relatively mild clinical type, to which three factors may have contributed—(*a*) a rather high proportion of older patients, (*b*) comparatively early admission to hospital and (*c*) a preponderance of purely tonsillar sites of the local lesion.

2. The proportions of toxic complications of the nervous and circulatory systems were relatively low.

3. The proportion of cases due to the infection with the gravis type of organism was high. Infections with this type provided the great bulk of deaths in the population.

4. In the older age groups there was a considerable excess of female cases. We have found that this conforms to the age and sex distribution of diphtheria in Scotland in three later years, and it appears that this phenomenon is one that must be expected at the present time.

PART II A

1. Constitution of Populations

In this part, the comparisons are mainly between the inoculated and the uninoculated portions of the population under study. It is necessary to define the meaning of the term "inoculated." The information was derived from summary cards and the inoculation history was not always precise. A comparison was therefore made between those patients who had satisfactory records of complete inoculation, those who had satisfactory records showing incomplete inoculation, and those whose history of inoculation was vague. The last group may or may not have had a complete series of inoculations. The information is summarised in Table K.

TABLE K

Inoculation Histories, Age Groups and Result in 1,023 Cases

Age Group	Inoculation History					
	Complete		Incomplete		Vague	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
0–4	135	–	10	–	57	–
5–9	363	2	33	2	108	–
10–14	192	2	7	–	70	–
15–24	20	–	–	–	23	1
25–	–	–	–	–	5	–
All Ages	710	4	50	2	263	1

It is evident that from the point of view of fatality no significant difference can be found between the three groups. In view of this finding it was decided that any patient with a history of inoculation should be regarded as inoculated. The term "immunised" has been avoided partly because of the apparent contradiction of describing diphtheria in the immunised and partly because of the nature of the histories. It is possible, though not proved, that if all inoculated patients had received a complete and fully documented course, the data would have been even more favourable to the inoculated group than they are.

The total number of inoculated patients in the inquiry was 1,023. The inquiry relates to a period when inoculation was being actively extended; while the proportion of inoculated persons to the total patients was roughly 1 in 4, the lack of precise information on the inoculation history of the child populations from which the patients were drawn does not permit us to estimate relative incidence rates.

2. Fatality

Reference to Appendix Table I shows that the population under study has the characteristic feature of populations including inoculated persons—i.e. the fatality rate from diphtheria in such persons was very low. In no age group did the fatality rate of the inoculated reach that of the uninoculated and the over-all difference, allowing for the varying age compositions of the populations, is entirely in favour of the inoculated.

3. Sex and Age

The age distribution of the inoculated patients differs markedly from that of the uninoculated. This was not unexpected because inoculation as a national measure had started only a little time before the survey was made so that the great proportion of inoculated persons would belong to pre-school and school populations. As a general picture, it may be stated that the uninoculated persons represent the population at all ages from which a certain group of younger persons had been abstracted by the process of pre-school and school inoculation. The relative proportions of cases (which did not represent the unknown rates of incidence) are given in Appendix Chart 5 which shows that at ages over 15, there were scarcely any inoculated patients to off-set against large numbers of uninoculated patients. For this reason, the main comparisons between inoculated and uninoculated patients have been limited to the age groups 0–4, 5–9 and 10–14, although in certain instances older age groups have been considered.

The beginnings of the female excess of cases were at age 4 in the uninoculated and at age 6 in the inoculated. Thereafter the excesses of females were approximately parallel in both inoculated and uninoculated patients for the same age groups. Examination of the data by areas (tables not reproduced) showed that the excess, though varying a little from one area to another, was general. Great stress cannot be laid on the slight postponement of the age at which the female excess starts in inoculated patients. It is not known, for instance, whether at some time an excess of male children may not have been inoculated, which of itself might account for the apparent equality of male and female patients in the inoculated group at ages 4 and 5.

Sex in itself did not affect the fate of inoculated children whether judged by fatality rate or by the complication rate. On this account, sex has not been used further as a means of sub-division of the two groups.

4. Duration of Illness on Admission

The inoculated patients tended to be admitted rather sooner in their illness than did the uninoculated (Appendix Table IV). The data have been examined by age groups in view of the different age constitutions of the populations in the comparison. For the three age groups under 15, the earlier admission of the inoculated, was found to be a suggestive finding. At ages over 15, the difference was found to be not significant. Comparison between the ages 0 to 14 and ages over 15 showed that the earlier admission in the first age group was highly significant. While formal significance is not always revealed by the data, it is an observation of considerable interest that the inoculated patient (and the younger patient) tend to be admitted earlier. It is possible that one reason for this is that the mere fact of an inoculation history connotes that the parents have exercised an interest in the health of their family. Possibly, therefore, such parents would take steps to secure treatment at a rather earlier stage of the disease than would parents whose interest in the welfare of their families has not extended so far as to secure inoculation.

5. Seasonal Incidence

The seasonal incidence table (Appendix Table III) gives a remarkably constant proportion of inoculated patients in the four seasons. The proportions are 23·5 per cent., 25·2 per cent., 24·3 per cent. and 23·2 per cent for each season. Deaths in the inoculated are concentrated in the first season of the year, a season which has also yielded the highest fatality rate in the uninoculated. In all seasons the relative sparing of deaths in the inoculated is evident.

6. Complications

As for recorded complications, the inoculated fared little better than did the uninoculated with an over-all incidence of 40·08 per cent. in the year as compared with 41·12 per cent. When studied by seasons, the main difference was in the first season when 44·12 per cent. of the inoculated had complications as against 49·27 per cent. of the uninoculated. For each season (and for the four seasons) the differences in complication incidence rates between the inoculated and the uninoculated were not of significance.

More importance is attached to the toxic complications; and their relative incidence, which is given in Appendix Table II, may be summarised in the following table which has been extracted therefrom :—

TABLE L

Incidence of Nervous and Circulatory Complications in Certain Age Groups

Age Group	Inoculated	Uninoculated
0–4	8·95%	12·52%
5–9	12·33%	14·51%
10–14	5·96%	11·01%

The above summary table brings out the relative sparing of toxic complications in inoculated patients when compared with uninoculated patients in the same age groups. The importance of age in this respect is shown by the fact that, of all inoculated cases (which includes a number outside the age groups given above), 2·16 per cent. developed nervous complications, 7·2 per cent. circulatory complications and 0·3 per cent. a combination of these two, giving a total of 9·66 per cent. with the stated toxic complications. A similar computation for all uninoculated patients, which includes a relatively high proportion of persons in older age groups, gives an incidence of 4·05 per cent. nervous complications, 4·8 per cent. circulatory complications and 0·77 per cent. with a combination of these two—a total of 9·62 per cent. But this apparent failure of the inoculated persons to benefit through lower incidence of toxic complications is corrected when the comparisons have been made by age groups as was done in Table L.

Even when inoculated patients developed toxic complications the outcome of their disease was much more favourable. This is immediately seen by reference to Appendix Table II. Nervous complications were not associated with any death in the inoculated population. Circulatory complications were associated with a fatality rate of 6·4 per cent. The corresponding fatality rates in the uninoculated population of patients were 5·26 per cent. and 27·88 per cent. In brief, the incidence of toxic complications was somewhat reduced and their association with death was most considerably reduced.

7. Type

The type distributions in the two populations are given in full in Appendix Table VI. Comparison of these distributions shows that the proportion of gravis infections at ages under 15 were 74 per cent. in the inoculated and 67·75 per cent. in the uninoculated. When compared in individual age groups, the following proportions have been obtained :—

TABLE M

Type Distributions by Age Groups in Inoculated and Uninoculated Patients

AGES		GRAVIS	INTERMEDIUS	MITIS
0–4	Inoculated	80·6%	12·7%	6·7%
	Uninoculated ...	70·1%	19·3%	10·6%
5–9	Inoculated	72·2%	19·0%	8·8%
	Uninoculated ...	65·9%	21·7%	12·4%
10–14	Inoculated	72·9%	16·6%	10·5%
	Uninoculated ...	66·2%	25·4%	8·4%

The significance of these differences has been examined and it has been found that at ages under 5 the differences are significant. They are not significant at ages 5–9 and 10–14. Taking the whole distribution, the relative excess of gravis infection in the inoculated is highly significant. This is considered to be a very important finding and the conclusion appears inevitable that inoculation is more potent in reducing infections with intermedius and mitis types than with the gravis type. In the populations studied, it is of interest that, in spite of the fact that among inoculated persons who developed diphtheria there was a significant excess of gravis infections, the ultimate outcome of their disease was still most significantly better than that of the uninoculated.

The association of type of organism with the incidence and fatality of toxic complications (Appendix Table II) has been mentioned, but some fuller reference may be made here. A combination of the figures of that table with those of Appendix Table VI gives the following proportions :—

TABLE N

Incidences of Toxic Complications by Inoculation History, Type and Age Group

TYPE	INOCULATED				UNINOCULATED			
	0–4	5–9	10–14	0–14	0–4	5–9	10–14	0–14
Gravis ...	10·2%	15·5%	5·5%	11·7%	16·3%	17·6%	17·8%	17·0%
Inter. ...	0·0%	16·4%	3·0%	10·6%	11·0%	15·3%	4·3%	11·2%
Mitis ...	(11·)	5·9%	0·0%	8·6%	11·2%	12·9%	8·5%	11·4%

Read in conjunction with Table M, Table N does not modify the main deduction from that preceding table, but amplifies it to some extent. The similarity of behaviour of intermedius and mitis infections in the uninoculated, and the distinction between them and gravis in this population, are clear. Inoculation did not affect the incidence rates of toxic complications in a uniform way, either when studied by age only, or by age and infecting type. On the whole, the proportional reduction in incidence was greatest in gravis infections, but in fact the reduction in this line of the table was largely achieved at ages 10–14. At ages under 5, toxic complications were not eliminated from gravis infections as they almost were from intermedius and mitis infections—the 11 shown in brackets representing one "toxic" case out of nine.

Little comment need be made on the fatality rates given in Appendix Table II ; they are consistent with what is already known of the lethal power of gravis strains in young uninoculated persons, when they affect the circulatory system.

8. Classification of Lesion

The distribution of cases by their various sites of local lesion is given in Appendix Table VII. Study of this table has shown that the inoculated group had a deficiency of pharyngeal and multiple sites (8·8 per cent.) as contrasted with the uninoculated (14 per cent.). This was largely counterbalanced by an excess of tonsillar sites in the inoculated (78·9 per cent.) as against the uninoculated (72·7 per cent.). The percentages just given are for all ages, and the difference between the inoculated and uninoculated groups is not quite constant when these are subdivided into finer age groups. At ages under 5 the relative percentages (inoculated first) are 78·7 and 67·9. At 5–9 years they are 80·4 and 78·0. At 10–14, they are 77·7 and 73·7, and at ages over 15, they are 70·8 and 72·8. This last age group is the only one in which there was an excess of tonsillar cases in the uninoculated. The significance of the differences between the various sites has been assessed for each age group. At ages under 5, the excess of tonsillar infections in the inoculated is very highly significant. In the other age groups the differences are not, for these limited ages, significant ; but when allowance is made for the differences in age distributions between inoculated and uninoculated patients, the excess of tonsillar cases in the inoculated is highly significant. This finding is considered to be of interest and importance. It appears that the inoculated patient tends to have a relatively localised infection and to be spared pharyngeal or multiple location of lesions which, as has already been remarked, are often associated with death. This relative circumscription of the lesion is attained concurrently with a proportionately high incidence of gravis infections in the inoculated, which has already been commented on as a significant finding. It may well be associated with the relative speed with which the inoculated have been found to be admitted to hospital.

The degree of toxæmia on admission is contrasted in Appendix Table VIII. Inoculated patients tended to arrive in hospital with a relatively mild degree of toxæmia. Their advantage from this aspect is significant; it may be associated partly with their slightly earlier admission and partly with the relative localisation of their lesions.

The percentage figures of the following table have been obtained from Appendix Table VIII.

TABLE O

Percentage Incidences of Degrees of Toxæmia

AGE GROUP	INOCULATED			UNINOCULATED		
	Mild	Moderate	Severe	Mild	Moderate	Severe
0–4	53·0%	38·6%	8·4%	41·7%	39·9%	18·4%
5–9	44·4%	44·8%	10·7%	40·7%	40·9%	18·4%
10–14	56·9%	34·6%	8·5%	43·5%	41·0%	15·5%
15–24	(42%)	(42%)	(16%)	45·6%	39·6%	14·8%
25–	(2/5)	(3/5)	—	47·6%	39·8%	12·6%

While this table shows sufficiently the general advantage of the inoculated, and the lessening of severity of toxæmia with increasing age, it is reproduced rather to draw attention to the relatively high degree of toxæmia in inoculated patients aged 5–9, higher than in the preceding or succeeding age group. On closer examination it was found that the apparent worsening at ages 5–9, compared with ages under 5, was not significant. The comparison of ages 5–9 and 10–14 showed highly significant improvement at 10–14; but this can be included in the general improvement with advancing age. The relatively high degree of toxæmia on admission at ages 5–9 is therefore regarded as having arisen by chance.

PART II B

Discussion

Although the original design of the inquiry was to elicit information regarding the effect of inoculation on the occurrence of diphtheria, not the least interesting aspect of the present report is its reflection of the natural behaviour of the disease in Scotland in 1942. The point which immediately emerges is the apparent mildness of the disease which in a series of 4,272 cases (of which only a quarter were immunised) produced a mortality rate of just less than 3 per cent. No doubt the very low fatality rate experienced by the inoculated serves to exaggerate the figure, but it would seem possible that diphtheria does not carry the severe prognosis which it formerly did; and this despite a high prevalence of *Gravis* infection. Nevertheless, even against this background of comparative mildness, the importance of the type of organism is not in doubt; for *Gravis* cases bore the highest fatality rate (4·3 per cent.) and gave rise to the highest rate of toxic complications (13·1 per cent.). The inability to draw a distinct line between Mitis and Intermedius infections is probably due to the small number of cases from which these other types were isolated.

For the series as a whole, the low fatality rate is naturally accompanied by a low rate of complications. There s no doubt that it has surprised us all to find that only 11 per cent. of the series showed, by the occurrence of certain complications, evidence of serious diphtheritic intoxication. Indeed such a finding caused us to adopt the most sceptical attitude of asking ourselves if this were really diphtheria ; and at first sight the large number of untyped cases lent some weight to such a hypothesis. As we have stated in the text, however, examination of the untyped cases has merely served to show that they are not dissimilar in any striking way from the remainder ; and, indeed, the figures for the incidence of nerve palsies and circulatory affections in the typed cases themselves shows in no uncertain manner that late toxic manifestations did not occur with any of the types to a very large extent. We are therefore forced to conclude that in Scotland in 1942 diphtheria had lost some of its power to cause severe and fatal disease.

This conclusion is further underlined when the extent of membrane formation is then examined ; for we find that three quarters of the cases showed a tonsillar membrane only. Now this is generally regarded as a mild clinical form of diphtheria, so that a high proportion of this clinical category in any series would seem to indicate one of three possibilities. First, the disease may be diagnosed at an early stage before spread can occur ; second, the population may possess some innate resisting power which inhibits spread ; third, the organism may be possessed of poor attacking devices. So far as the last is concerned all the evidence at our disposal suggests that the diphtheria bacilli prevalent in Scotland were in no way different from the bacteria affecting the rest of the country. As to the first point the mean duration of illness on admission was approximately three days, and one-third of the cases were four days ill or more. Such figures cannot be regarded as unsatisfactory in a disease characterised by an insidious onset ; but they also permit a contention that, on average, time had been allowed for extension of membrane and toxic absorption to occur. Although, therefore, it must always remain difficult to separate the different stresses in the host-parasite relationship, the findings would suggest that the host in Scotland has acquired, from his experience of the past, some capacity for mitigating the attack of the diphtheria bacillus.

To make such a suggestion from the survey of the material is not perhaps unimportant to our main purpose. It seems a reasonable contention to argue that the effects of immunisation would be seen to best advantage where the disease was severe. Under such circumstances one would expect the benefits to the inoculated to be more obvious. Against such a background we feel that the comparison of inoculated and uninoculated shows a surprising superiority of the former. So far as the incidence of toxic complications is concerned, age for age the inoculated show a lower rate ; and when attention is directed to the patients with *Gravis* infections the reduction is quite striking. Perhaps the most impressive figures are the fatality rates in the *Gravis* infection which suffered toxic complications ; for the inoculated the figure is 9·2 per cent., for the uninoculated, 27·1 per cent. Finally, the lesion produced differed, particularly in those under 5 years of age, for in 79 per cent. of the inoculated it was confined to the tonsils whereas in the uninoculated only 68 per cent. were so localised.

As an objective comment on the preceding paragraphs, it is interesting to compare in a broad fashion, the age-distributions in the present series with that which obtained in 1936–38. The corrected notifications of diphtheria in Scotland for that period, when immunisation was not practised to any extent, have been abstracted from the Annual Reports of the Department of Health. In the accompanying table they are placed alongside the equivalent figure for the present series :—

TABLE P

Age Group Years	1936–38		1942			
			All Cases		Uninoculated Only	
	Cases	Proportion	Cases	Proportion	Cases	Proportion
0–4	6,913	116	1,145	93	943	80
–14	16,652	279	1,899	154	1,126	95
15 –	5,964	100	1,228	100	1,180	100

Now even allowing for the roughness of the method, the discrepancy between the distributions is very striking. The great reduction in the number of cases under 15 years and especially in the age group 5–14 years can only be ascribed to the effect of immunisation.

This survey, therefore, despite the drawbacks (from the point of view of a strict comparison) of the period in which it was made, leaves no room for doubt of the efficacy of diphtheria immunisation. Further, it supports the value of continuous bacteriological analysis of the diphtheria population ; for the finding that there was a slight excess of *Gravis* infections in the inoculated suggests that when this strain is in the ascendent some failures in protection may be expected.

Summary of Part II

1. The inquiry included 1,023 patients with some history of inoculation and 3,249 patients with no history of inoculation. The respective fatality rates were 0·68 per cent. (7 deaths) and 3·69 per cent. (120 deaths).

2. The age distribution of the inoculated population was inevitably different from that of the uninoculated because inoculation had recently become a national measure and was largely applied to children. Sex differences were apparently unimportant.

3. Patients who had been inoculated tended to be admitted earlier in their disease. This was partly associated with a lower average age.

4. Inoculated patients had, compared with the uninoculated, a slightly lower incidence rate of complications and a significantly lower incidence rate of toxic complications. Such complications as they had were seldom fatal.

5. Inoculated patients had a significantly higher proportion of *Gravis* infections, suggesting that prior to the period under review inoculation induced a less solid immunity against this type than against *Intermedius* and *Mitis* types.

6. Inoculated patients had a significantly higher proportion of tonsillar infections and significantly less pharyngeal and multiple infections. Their degree of toxæmia, assessed clinically on admission to hospital, was significantly less.

References

Carter, H. S. (1944). *J. Hygiene*, 43, 341.

Department of Health for Scotland (1944). *Sulphonamides in the Treatment of Meningococcal Meningitis.* (Report to the Scientific Advisory Committee.)

Ker, C. B. (1909). *Infectious Diseases.* London.

McKinlay, P. L. (1947). *Health Bulletin* (*C.M.O., Department of Health for Scotland*), 5, 73.

McLeod, J. W., Orr, J. W., and Woodcock, H. E. de C. (1939). *J. Path. & Bact.*, 48, 99.

APPENDIX I

Scientific Advisory Committee Diphtheria Record

1. Name ....
2. Address ....
....
3. Date of Birth.. 4. Sex....................
5. HOSPITAL ....
6. Date of Admission..
7. No. of days in Hospital..
8. Result of Swab before Admission ☐ Negative ☐ Positive
9. Result of Swab after Admission ☐ Negative ☐ Positive
10. Type ....
11. Days ill before Admission..
12. Clinical Diphtheria ? ☐ Yes ☐ No
13. Cultural Diphtheria only ? ☐ Yes ☐ No
14. CLASSIFICATION OF LESION Extent

☐ (1) Anterior Nasal .... +
☐ (2) Laryngeal.............................. +
☐ (3) ,, ... + +
☐ (4) ,, ... + + +
☐ (5) Tonsillar .... +
☐ (6) ,, ... + +
☐ (7) Pharyngeal (*a*) Pillars .... +
☐ (8) ,, ,, ... + +
☐ (9) ,, (*b*) Pharynx .... +
☐ (10) ,, ,, ... + +
☐ (11) ,, (*c*) Palate .... +
☐ (12) ,, ,, ... + +
☐ (13) ,, (*d*) Uvula .... +
☐ (14) ,, (*e*) Post-nasal Mucosa .... +
☐ (15) ,, ,, ... + +
☐ (16) ,, ,, ... + + +
☐ (17) Non-respiratory

Approx. date of Immunisation..
Place of Immunisation ....

Front

15. Toxæmia ☐ Mild
☐ Moderate
☐ Severe

16. Complications (including immediate complications)..
....
....
....
....

17. Serum Dosage .... units IM
.... units IV

18. Result ☐ Recovery
☐ Death (date ....)

19. Final Diagnosis ☐ (1) Diphtheria
☐ (2) Bacteriological Diphtheria
☐ (3) Not Diphtheria (......................................)

20. IMMUNISATION RECORD

	First Series			Later Series		
	1st	2nd	3rd	1st	2nd	3rd
Date	....	....	....	....	....	....
Dose	....	....	....	....	....	....
Maker	....	....	....	....	....	....
Material	....	....	....	....	....	....

21. Schick Tests

Date			
Result			

22. Reactions to Toxoid ....
....

23. Remarks ....
....
....
....
....

Initials..............................

APPENDIX TABLES

TABLE I

Sex, Age Groups, Inoculation History and Result—All Cases

AGE GROUP		INOCULATED		UNINOCULATED		TOTALS		
		Males	Females	Males	Females	Males	Females	Both Sexes
0–4	Cases ...	106	96	468	475	574	571	1,145
	Deaths ...	0	0	36	31	36	31	67
	Fat. Rate	–	–	7·69%	6·53%	6·27%	5·43%	5·85%
5–9	Cases ...	238	266	359	413	597	679	1,276
	Deaths ...	1	3	12	16	13	19	32
	Fat. Rate	0·42%	1·13%	3·34%	3·87%	2·18%	2·80%	2·51%
10–14	Cases ...	104	165	151	203	255	368	623
	Deaths ...	0	2	8	4	8	6	14
	Fat. Rate	–	1·21%	5·30%	1·97%	3·14%	1·63%	2·25%
15–24	Cases ...	10	33	237	546	247	579	826
	Deaths ...	0	1	3	2	5	3	8
	Fat. Rate	–	(3%)	2·11%	0·37%	2·02%	1·52%	0·97%
25—	Cases ...	2	3	98	299	100	302	402
	Deaths ...	0	0	3	3	3	3	6
	Fat. Rate	–	–	3·06%	1·00%	3·00%	0·99%	1·49%
ALL AGES	Cases ...	460	563	1,313	1,936	1,773	2,499	4,272
	Deaths ...	1	6	64	56	65	62	127
	Fat. Rate	0·22%	1·07%	4·87%	2·89%	3·67%	2·48%	2·97%

TABLE II

Toxic Complications, Age Groups, Type of Organism, Inoculation History and Result—477 Patients

AGES	TYPES	INOCULATED								UNINOCULATED								TOTALS								FATALITY RATES
		Nervous		Circulatory		N. + C*.		Total		Nervous		Circulatory		N. + C.		Total		Nervous		Circulatory		N. + C.		Total		
		C†	D‡	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	
0–4	Gravis	4	–	7	–	–	–	11	–	19	2	50	27	6	2	75	31	23	2	57	27	6	2	86	31	36·0%
	Intermedius ...	–	–	–	–	–	–	–	–	4	–	9	2	1	–	14	2	4	–	9	2	1	–	14	2	(14%)
	Mitis	–	–	1	–	–	–	1	–	3	1	3	1	1	–	7	2	3	1	4	1	1	–	8	2	(25%)
	Unstated	2	–	4	–	–	–	6	–	15	–	15	4	2	–	32	4	17	–	19	4	2	–	38	4	(11%)
	Total	6	–	12	–	–	–	18	–	41	3	77	34	10	2	128	39	47	3	89	34	10	2	146	39	26·7%
	Fatality Rate ...	–	–	–	–	–	–	–	–	(7%)		44·2%		(20%)		30·5%		(6%)		38·2%		(20%)		26·7%		...
5–9	Gravis	8	–	32	3	3	1	43	4	25	1	30	12	11	3	66	16	33	1	62	15	14	4	109	20	18·3%
	Intermedius ...	1	–	11	–	–	–	12	–	8	–	10	2	1	–	19	2	9	–	21	2	1	–	31	2	(6%)
	Mitis	–	–	2	–	–	–	2	–	7	–	7	–	–	–	14	–	7	–	9	–	–	–	16	–	...
	Unstated	1	–	7	–	1	–	9	–	9‡	–	16	1	1	–	26	1	10	–	23	1	2	–	35	1	(3%)
	Total	10	–	52	3	4	1	66	4	49	1	63	15	13	3	125	19	59	1	115	18	17	4	191	23	12·0%
	Fatality Rate ...	–	–	5·8%		–	–	6·1%		(2%)		23·8%		(23%)		15·2%		1·7%		15·7%		(24%)		12·0%		...
10–14	Gravis	2	–	6	2	–	–	8	2	9	2	20	5	3	1	32	8	11	2	26	7	3	1	40	10	(25%)
	Intermedius ...	–	–	1	–	–	–	1	–	–	–	3	–	–	–	3	–	–	–	4	–	–	–	4	–	...
	Mitis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	...
	Unstated	1	–	6	–	–	–	7	–	1	–	6	–	–	–	7	–	2	–	12	–	–	–	14	–	...
	Total	3	–	13	2	–	–	16	2	10	2	29	5	3	1	42	8	13	2	42	7	3	1	58	10	17·2%
	Fatality Rate ...	–	–	(15%)		–	–	(12%)		(20%)		(17%)		–	–	(19%)		(15%)		(17%)		–	–	17·2%		...
15–24	Gravis	2	–	1	–	–	–	3	–	15	1	15	2	6	2	36	5	17	1	16	2	6	2	39	5	(13%)
	Intermedius ...	–	–	–	–	–	–	–	–	3	–	3	–	–	–	6	–	3	–	3	–	–	–	6	–	...
	Mitis	–	–	–	–	–	–	–	–	–	–	1	–	–	–	1	–	–	–	1	–	–	–	1	–	...
	Unstated	1	–	–	–	–	–	1	–	3	–	7	–	–	–	10	–	4	–	7	–	–	–	11	–	...
	Total	3	–	1	–	–	–	4	–	21	1	26	2	6	2	53	5	24	1	27	2	6	2	57	5	8·8%
	Fatality Rate ...	–	–	–	–	–	–	–	–	(5%)		(8%)		–	–	9·4%		(4%)		(7%)		–	–	8·8%		...
25—	Gravis	–	–	–	–	–	–	–	–	9	–	7	1	–	–	16	1	9	–	7	1	–	–	16	1	(6%)
	Intermedius ...	–	–	–	–	–	–	–	–	–	–	3	1	–	–	3	1	–	–	3	1	–	–	3	1	...
	Mitis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	...
	Unstated	–	–	–	–	–	–	–	–	3	–	3	–	–	–	6	–	3	–	3	–	–	–	6	–	...
	Total	–	–	–	–	–	–	–	–	12	–	13	2	–	–	25	2	12	–	13	2	–	–	25	2	(8%)
	Fatality Rate ...	–	–	–	–	–	–	–	–	–	–	(15%)		–	–	(8%)		–	–	(15%)		–	–	(8%)		...
All Ages	Gravis	16	–	46	5	3	1	65	6	77	6	122	47	26	8	225	61	93	6	168	52	29	9	290	67	23·1%
	Intermedius ...	1	–	12	–	–	–	13	–	15	–	28	5	2	–	45	5	16	–	40	5	2	–	58	5	8·6%
	Mitis	–	–	3	–	–	–	3	–	10	1	11	1	1	–	22	2	10	1	14	1	1	–	25	2	(8%)
	Unstated	5	–	17	–	1	–	23	–	31	–	47	5	3	–	81	5	36	–	64	5	4	–	104	5	4·8%
	Total	22	–	78	5	4	1	104	6	133	7	208	58	32	8	373	73	155	7	286	63	36	9	477	79	16·6%
	Fatality Rate ...	–	–	6·4%		–	–	5·8%		5·3%		27·9%		(25%)		19·6%		4·5%		22·0%		(25%)		16·6%		...

* N. + C. : Nervous plus circulatory complications in the same patient. † C. : Cases. ‡ D. : Deaths.

TABLE III

Seasons, Complications, Inoculation History and Result—All Cases

PERIOD		INOCULATED			UNINOCULATED			TOTALS		
		C–	C+	Total	C–	C+	Total	C–	C+	Total
FIRST QUARTER	Cases	152	120	272	449	436	885	601	556	1,157
	Deaths	0	5	5	10	38	48	10	43	53
	Fatality Rate ...	–	4·17%	1·84%	2·23%	8·72%	5·42%	1·66%	7·73%	4·58%
SECOND QUARTER	Cases	141	96	237	411	296	707	552	392	944
	Deaths	0	0	0	1	22	23	1	22	23
	Fatality Rate ...	–	–	–	0·24%	7·43%	3·25%	0·18%	5·61%	2·44%
THIRD QUARTER	Cases	117	93	210	373	280	653	490	373	863
	Deaths	0	1	1	1	14	15	1	15	16
	Fatality Rate ...	–	1·08%	0·48%	0·27%	5·00%	2·30%	0·20%	4·02%	1·85%
FOURTH QUARTER	Cases	203	101	304	680	324	1,004	883	425	1,308
	Deaths	0	1	1	7	27	34	7	28	35
	Fatality Rate ...	–	0·99%	0·33%	1·03%	8·33%	3·39%	0·79%	6·59%	2·68%
TOTAL FOR YEAR	Cases	613	410	1,023	1,913	1,336	3,249	2,526	1,746	4,272
	Deaths	–	7	7	19	101	120	19	108	127
	Fatality Rate ...	–	1·71%	0·68%	0·99%	7·56%	3·69%	0·75%	6·19%	2·97%

C–: Without complications.   C+: With complications.

TABLE IV

Duration of Illness on Admission, Age Groups, Inoculation History and Result—All Cases

Age Group		INOCULATED								UNINOCULATED								ALL CASES							
		Number of Days Ill on Admission								Number of Days Ill on Admission								Number of Days Ill on Admission							
		1	2	3	4	5	6+	*Un.	Total	1	2	3	4	5	6+	*Un.	Total	1	2	3	4	5	6+	*Un.	Total
0–4	Cases ...	25	65	43	29	20	17	3	202	106	234	219	150	89	111	34	943	131	299	262	179	109	128	37	1,145
	Deaths ...	–	–	–	–	–	–	–	–	2	9	15	20	9	11	1	67	2	9	15	20	9	11	1	67
	Fat. Rate	–	–	–	–	–	–	–	–	1·9%	3·8%	6·8%	13·3%	10·1%	9·9%	(3%)	7·10%	1·5%	3·0%	5·7%	11·2%	8·3%	8·6%	(3%)	5·85%
5–9	Cases ...	57	166	131	78	26	37	9	504	86	259	177	111	54	71	14	772	143	425	308	189	80	108	23	1,276
	Deaths ...	–	1	2	1	–	–	–	4	1	5	6	7	3	4	2	28	1	6	8	8	3	4	2	32
	Fat. Rate	–	0·6%	1·5%	1·3%	–	–	–	0·79%	1·2%	1·9%	3·4%	6·3%	5·6%	5·6%	(14%)	3·63%	0·7%	1·4%	2·6%	4·2%	3·7%	3·7%	(9%)	2·51%
10–14	Cases ...	22	90	63	44	21	24	5	269	30	113	100	49	28	29	5	354	52	203	163	93	49	53	10	623
	Deaths ...	–	1	–	–	–	1	–	2	1	3	5	1	–	1	1	12	1	4	5	1	–	2	1	14
	Fat. Rate	–	1·1%	–	–	–	(4%)	–	0·7%	(3%)	2·7%	5·0%	(2%)	–	(3%)	(20%)	3·39%	1·9%	2·0%	3·1%	1·1%	–	3·8%	(10%)	2·25%
15–24	Cases ...	10	11	10	6	4	–	2	43	73	190	213	138	70	87	12	783	83	201	223	144	74	87	14	826
	Deaths ...	–	–	1	–	–	–	–	1	–	2	2	–	–	3	–	7	–	2	3	–	–	3	–	8
	Fat. Rate	–	–	(10%)	–	–	–	–	(2%)	–	1·1%	0·9%	–	–	3·4%	–	0·89%	–	1·0%	1·3%	–	–	3·4%	–	0·97%
25–	Cases ...	1	–	3	1	–	–	–	5	26	78	107	77	37	57	15	397	27	78	110	78	37	57	15	402
	Deaths ...	–	–	–	–	–	–	–	–	–	1	3	–	–	–	2	6	–	1	3	–	–	–	2	6
	Fat. Rate	–	–	–	–	–	–	–	–	–	1·3%	2·8%	–	–	–	(13%)	1·51%	–	1·3%	2·7%	–	–	–	(13%)	1·49%
All Ages	Cases ...	115	332	250	158	71	78	19	1,023	321	874	816	525	278	355	80	3,249	436	1,206	1,066	683	349	433	99	4,272
	Deaths ...	–	2	3	1	–	1	–	7	4	20	31	28	12	19	6	120	4	22	34	29	12	20	6	127
	Fat. Rate	–	0·6%	1·2%	0·6%	–	1·3%	–	0·68%	1·2%	2·29%	3·80%	5·33%	4·3%	5·4%	7·5%	3·69%	0·9%	1·82%	3·19%	4·25%	3·43%	4·62%	6·1%	2·97%

* Unstated

TABLE V

Type of Organism, Duration of Illness on Admission and Result—All Cases

Type		Days Duration of Illness on Admission							
		1	2	3	4	5	6 or over	Unstated	Totals
Gravis	Cases	241	559	554	390	189	224	62	2,219
	Deaths	3	19	27	23	8	11	5	96
	Fatality Rate ...	1·25%	3·40%	4·87%	5·90%	4·23%	4·91%	8·1%	4·33%
Intermedius ...	Cases	72	173	173	89	49	71	13	640
	Deaths	–	–	1	1	1	2	–	5
	Fatality Rate ...	–	–	0·58%	1·1%	2·0%	2·8%	–	0·78%
Mitis	Cases	14	82	96	64	27	39	6	328
	Deaths	–	–	1	2	1	1	–	5
	Fatality Rate ...	–	–	1·0%	3·2%	(4%)	2·6%	–	1·52%
Unstated or Untyped	Cases	109	392	243	140	84	99	18	1,085
	Deaths	1	3	5	3	2	6	1	21
	Fatality Rate ...	0·92%	0·77%	2·06%	2·14%	2·4%	6·06%	(6%)	1·94%
All Types	Cases	436	1,206	1,066	683	349	433	99	4,272
	Deaths	4	22	34	29	12	20	6	127
	Fatality Rate ...	0·92%	1·82%	3·19%	4·25%	3·44%	4·62%	6·06%	2·97%

TABLE VI

Type of Organism, Age Groups, Inoculation History and Result—All Cases

AGE GROUP		INOCULATED					UNINOCULATED					TOTALS				
		Gravis	Inter-medius	Mitis	Un-stated	Total	Gravis	Inter-medius	Mitis	Un-stated	Total	Gravis	Inter-medius	Mitis	Un-stated	All Types
0–4	Cases ...	108	17	9	68	202	461	127	70	285	943	569	144	79	353	1,145
	Deaths	0	0	0	0	0	44	2	5	16	67	44	2	5	16	67
	Fatality Rate	–	–	–	–	–	9·54%	1·57%	7·1%	5·61%	7·10%	7·73%	1·39%	6·3%	4·53%	5·85%
5–9	Cases ...	278	73	34	119	504	376	124	71	201	772	654	197	105	320	1,276
	Deaths	4	0	0	0	4	24	2	0	2	28	28	2	0	2	32
	Fatality Rate	1·44%	–	–	–	0·79%	6·38%	1·61%	–	1·00%	3·63%	4·28%	1·02%	–	0·62%	2·51%
10–14	Cases ...	145	33	21	70	269	180	69	23	82	354	325	102	44	152	625
	Deaths	2	0	0	0	2	11	0	0	1	12	13	0	0	1	14
	Fatality Rate	1·38%	–	–	–	0·74%	6·11%	–	–	1·2%	3·39%	4·00%	–	–	0·66%	2·25%
15–24	Cases ...	29	4	2	8	43	422	129	65	167	783	451	133	67	175	826
	Deaths	1	0	0	0	1	6	0	0	1	7	7	0	0	1	8
	Fatality Rate	3%	–	–	–	2%	1·42%	–	–	0·60%	0·89%	1·55%	–	–	0·57%	0·97%
25 –	Cases ...	2	1	1	1	5	218	63	32	84	397	220	64	33	85	402
	Deaths	0	0	0	0	0	4	1	0	1	6	4	1	0	1	6
	Fatality Rate	–	–	–	–	–	1·85%	1·6%	–	1·2%	1·51%	1·82%	1·6%	–	1·2%	1·49%
All Ages	Cases ...	562	128	67	266	1,023	1,657	512	261	819	3,249	2,219	640	328	1,085	4,272
	Deaths	7	0	0	0	7	89	5	5	21	120	96	5	5	21	127
	Fatality Rate	1·25%	–	–	–	0·68%	5·37%	0·98%	1·92%	2·56%	3·69%	4·33%	0·78%	1·52%	1·94%	2·79%

TABLE VII

Classification of Local Lesion, Age Groups, Inoculation History and Result—All Cases

AGE GROUP		INOCULATED				UNINOCULATED				ALL CASES			
		Tonsillar	Pharyngeal + Multiple	Other Sites	All Sites	Tonsillar	Pharyngeal + Multiple	Other Sites	All Sites	Tonsillar	Pharyngeal + Multiple	Other Sites	All Sites
0–4	Cases ...	159	14	29	202	640	126	177	943	799	140	206	1,145
	Deaths ...	–	–	–	–	21	35	11	67	21	35	11	67
	Fatality Rate	–	–	–	–	3·28%	27·8%	6·2%	7·10%	2·63%	25·0%	5·3%	5·85%
5–9	Cases ...	405	46	53	504	602	99	71	772	1,007	145	124	1,276
	Deaths ...	1	3	–	4	7	19	2	28	8	22	2	32
	Fatality Rate	0·2%	(7%)	–	0·79%	1·16%	19·2%	2·8%	3·63%	7·94%	15·2%	1·6%	2·51%
10–14	Cases ...	209	24	36	269	261	44	49	354	470	68	85	623
	Deaths ...	–	2	–	2	6	6	–	12	6	8	–	14
	Fatality Rate	–	(8%)	–	0·7%	2·3%	(14%)	–	3·4%	1·3%	11·8%	–	2·25%
15–24	Cases ...	31	6	6	43	587	117	79	783	618	123	85	826
	Deaths ...	–	1	–	1	3	4	–	7	3	5	–	8
	Fatality Rate	–	(17%)	–	(2%)	0·51%	3·4%	–	0·89%	0·49%	4·1%	–	0·97%
25 –	Cases ...	3	–	2	5	272	68	57	397	275	68	59	402
	Deaths ...	–	–	–	–	–	3	3	6	–	3	3	6
	Fatality Rate	–	–	–	–	–	4·4%	5·3%	1·5%	–	4·4%	5·1%	1·49%
All Ages	Cases ...	807	90	126	1,023	2,362	454	433	3,249	3,169	544	559	4,272
	Deaths ...	1	6	–	7	37	67	16	120	38	73	16	127
	Fatality Rate	0·12%	6·7%	–	0·68%	1·57%	14·76%	3·70%	3·69%	1·20%	1·34%	2·86%	2·97%

TABLE VIII

Degree of Toxæmia on Admission, Age Groups, Inoculation History and Result—All Cases

AGE GROUP		INOCULATED				UNINOCULATED				TOTALS			
		Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
0–4	Cases ...	107	78	17	202	393	376	174	943	500	454	191	1,145
	Deaths ...	–	–	–	–	4	11	52	67	4	11	52	67
	Fatality Rate	–	–	–	–	1·02%	2·93%	29·9%	7·10%	0·80%	2·42%	27·2%	5·85%
5–9	Cases ...	224	226	54	504	314	316	142	772	538	542	196	1,276
	Deaths ...	–	–	4	4	1	3	24	28	1	3	28	32
	Fatality Rate	–	–	7·4%	0·79%	0·32%	0·95%	16·9%	3·63%	0·19%	0·55%	14·3%	2·51%
10–14	Cases ...	153	93	23	269	154	145	55	354	307	238	78	623
	Deaths ...	–	–	2	2	1	2	9	12	1	2	11	14
	Fatality Rate	–	–	9%	0·74%	0·65%	1·38%	16·4%	3·39%	0·33%	0·84%	14·1%	2·25%
15–24	Cases ...	18	18	7	43	357	310	116	783	375	328	123	826
	Deaths ...	–	–	1	1	1	–	6	7	1	–	7	8
	Fatality Rate	–	–	–	2%	0·28%	–	5·17%	0·89%	0·27%	–	5·69%	0·97%
25 –	Cases ...	2	3	–	5	189	158	50	397	191	161	50	402
	Deaths ...	–	–	–	–	3	–	3	6	3	–	3	6
	Fatality Rate	–	–	–	–	1·59%	–	6%	1·51%	1·57%	–	6%	1·49%
All Ages	Cases ...	504	418	101	1,023	1,407	1,305	537	3,249	1,911	1,723	638	4,272
	Deaths ...	–	–	7	7	10	16	94	120	10	16	101	127
	Fatality Rate	–	–	6·93%	0·68%	0·71%	1·23%	17·5%	3·69%	0·52%	0·93%	15·83%	2·97%

Chart 1
(*See* Table F)

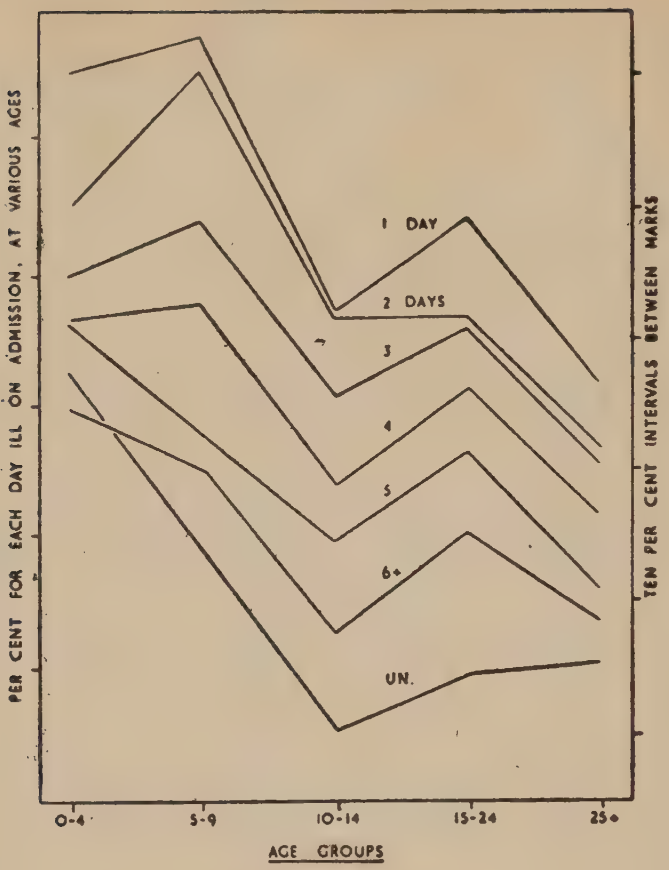


Chart 2
(*See* Table V)

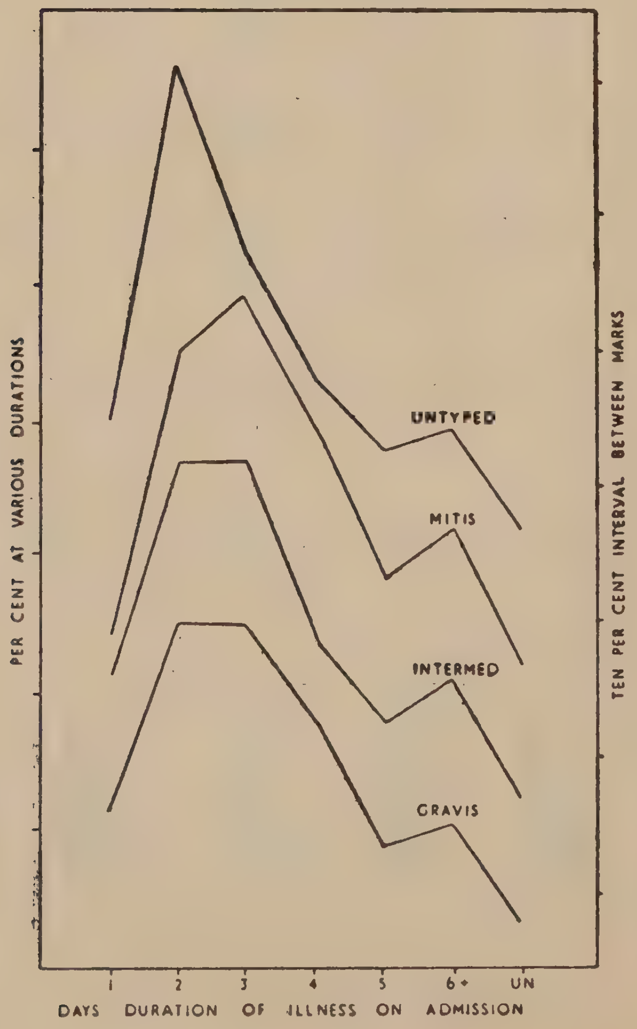


Chart 3
(*See* Table VI)

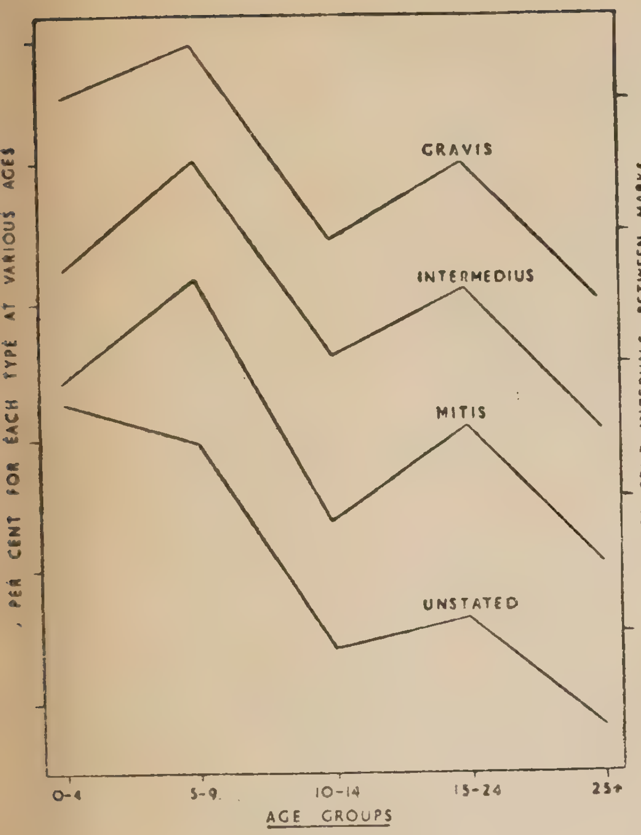


Chart 4
(*See* Table G)

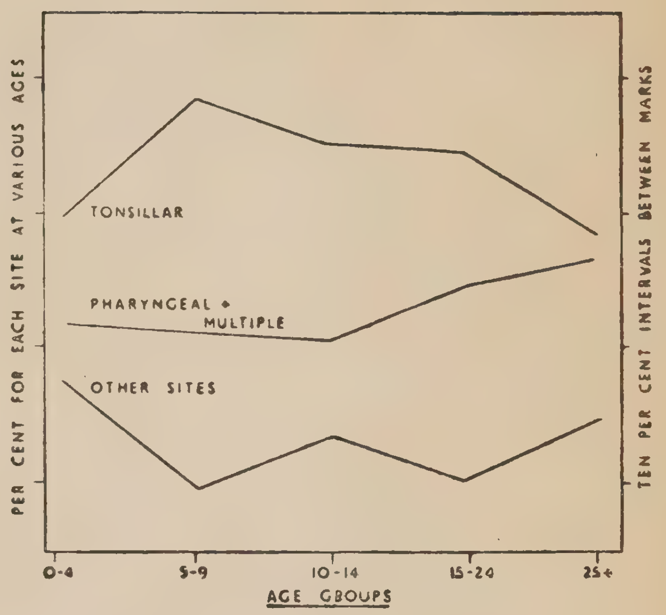
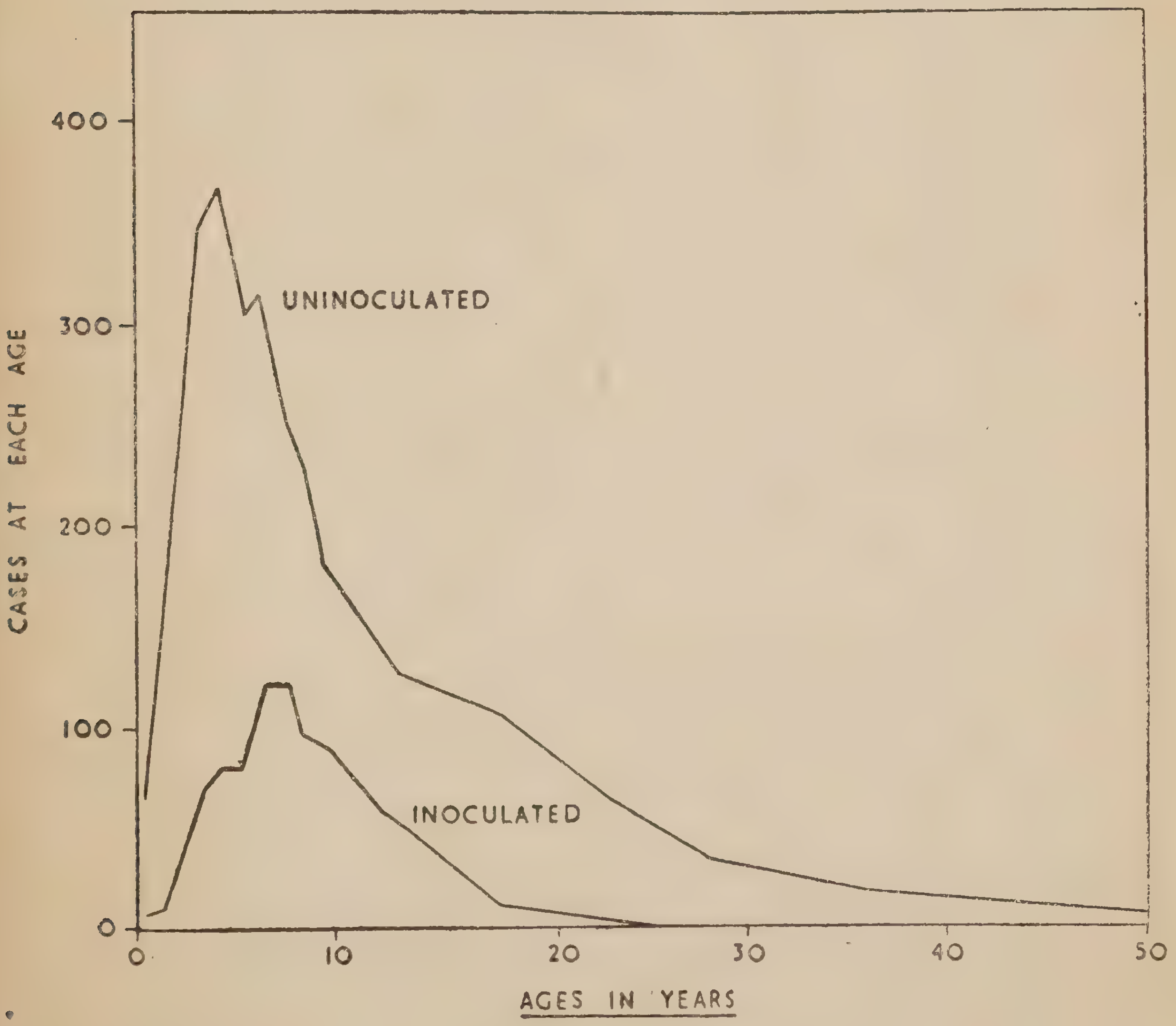


Chart 5
(Age distributions of inoculated and uninoculated)



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Cerebro-Spinal Fever

Report by the Infectious Diseases Sub-Committee of the Scientific Advisory Committee, on a Comparison of Penicillin and Sulphonamide Treatments of Meningococcal Meningitis in Young Children

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FOREWORD

The Sub-Committee on Infectious Diseases has continued its study of the treatment of meningococcal meningitis in young children. The importance of this investigation lies in the fact that this form of meningitis has a high fatality rate and has become unusually prevalent in recent years. Since the epidemic of 1940-41, it has maintained a persistently high endemic level in Scotland, more so than in other parts of Great Britain.

The first Report of the Sub-Committee, published in 1944, showed that sulphonamide treatment was a distinct advance on other therapeutic methods. Penicillin having become increasingly available since then, it was decided to make a straight comparison between it and the sulphonamides in the treatment of meningococcal meningitis in children under five years of age. The results are now set out in this, the second Report.

The conclusion reached as regards penicillin is that the result of its administration does not support the hope entertained that it would prove to be more efficacious than sulphonamide treatment. The comparison made between the two methods is distinctly in favour of the latter. At the same time, there has emerged the definite possibility that combined treatment with both products will yield results superior to those obtained by the use of either method of treatment alone. Accordingly, the Sub-Committee have now embarked upon further investigations along these lines.

A. S. M. Macgregor

Chairman,
Scientific Advisory Committee.

St Andrew's House,
Edinburgh.
August, 1947.

The Sub-Committee on Infectious Diseases Research

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CEREBRO-SPINAL FEVER

A Comparison of Penicillin and Sulphonamide Treatments of Meningococcal Meningitis in Young Children

In the previous report by this Committee on sulphonamides in the treatment of meningococcal meningitis (1) it was observed (in Table II of that Report) that, even with treatment considered adequate, the fatality rate of this infection remained high at the extremes of life. If any improvement were to be looked for, either by refinement in sulphonamide technique or through the introduction of new drugs, the criterion of success would therefore be found in the results in the extreme age groups.

Soon after the publication of the first Report, limited supplies of penicillin became available for the treatment of grave infections in the civil population. Consideration was given to the possibility of making a comparison of the relative efficacy of treatments with penicillin and with sulphonamides. By this time, the epidemic incidence of meningococcal meningitis which had been heavy in 1940-1 had much lessened and it was decided to limit the comparison to patients under the age of 5 years. There was no point in including patients over the age of 40, in whom the residual fatality rate had remained high in spite of sulphonamide treatment, as patients in that age group were, by this time, few.

The comparison could have been between two or three of the following groups :

(*a*) patients treated with penicillin only ;
(*b*) patients treated with sulphonamides only ;
(*c*) patients treated with penicillin plus sulphonamides.

It was decided to make the main comparison between groups (*a*) and (*b*) above. Consideration was given to the questions of whether the age groups 0–1 and 1–4 should be treated as separate populations and whether patients should be allocated to treatments (*a*) and (*b*) in alternate order or by random selection. It was decided to treat the age group 0–4 as one population and treat patients in alternate order by time of admission. This strict order was to some extent upset by individual cases where the patient was admitted with a clear history of having been given a sulphonamide prior to admission. If such patients were to be treated with penicillin from the time of admission to hospital, they could not be regarded as having had only one form of treatment. It was therefore thought better, in a number of such cases, to continue the patient as a sulphonamide-treated case even though he was due to become a penicillin-treated case.

From the outset it was realised that it might be difficult to obtain clear-cut results because of the relatively small number of patients available in a post-epidemic period. Patients receiving sulphonamide treatment at age under 1 had had a fatality rate of 28 per cent. and at ages 1–4 a fatality rate of 19 per cent. Even if penicillin were to reduce the fatality rate to zero, a group of infants aged under 1 comprising about 30 individual patients would be necessary to demonstrate formally the significance of the findings, and a group of about 40 at ages 1–4. It was not expected that penicillin would achieve a reduction of the rate to zero and correspondingly larger groups of patients would be necessary if the inquiry were to be pursued to a formal conclusion.

Schedules of treatment were agreed before the clinical trials started ; great help was given in drawing up the penicillin schedule by Dr Challinor and

Dr Duguid of the Department of Bacteriology, University of Edinburgh, and this help is gratefully acknowledged. The schedules were as follows :—

Sulphonamide (preferably sulphathiazole, but other active drug not excluded).

Age under 1—0·5 gramme I.V. or I.M. on admission.
4·0 grammes orally in first 24 hours, divided into 3-hourly doses.
3·0 grammes orally in each subsequent 24 hours, in 3-hourly doses.
Ages 1–4— 0·5 gramme I.V. or I.M. on admission.
4·5 grammes orally in first 24 hours, divided into 3-hourly doses.
4·5 grammes orally in each subsequent 24 hours, in 3-hourly doses.

Termination of sulphonamide treatment to be decided according to progress of the patient.

Penicillin

Age under 1—	1st day	2nd day	3rd day	4th day
Systemic	200,000	—	—	—
Intrathecal	5,000	5,000	5,000	5,000

Ages 1–4—	1st day	2nd day	3rd day	4th day
Systemic	400,000	—	—	—
Intrathecal	10,000	10,000	10,000	10,000

Systemic administration to be either by 3-hourly I.V. injection or by continuous I.M. drip. Termination of penicillin treatment to be at the end of the 4th day ; but if the clinical condition were to recur or the cerebro-spinal fluid show persistence of organisms, turbidity or a high protein level, a further course of intrathecal penicillin would be given. Intraventricular or intracisternal injection to be employed if retrograde diffusion of penicillin were considered difficult or impossible.

In consequence of later discussion and the development of knowledge of penicillin administration, a number of penicillin-treated patients did not receive systemic penicillin, reliance being placed entirely on intrathecal injection.

As the inquiry progressed a few patients were judged to have failed to improve on one method of treatment and were transferred to the other method ; there was one sulphonamide failure transferred to penicillin treatment, and there were three penicillin failures transferred to sulphonamide treatment. All four patients eventually recovered from their meningococcal infections and their status in the inquiry has been closely considered. There was a strong impression on the clinical observers that the failure of the first treatment tried was so grave that only by resort to the second treatment was the patient's life saved. It was decided that the exclusion of these cases from the results of the inquiry would not give a true picture of the relative therapeutic efficacy of penicillin and sulphonamides. Each of the four cases has accordingly been reckoned twice in Table I, giving one sulphonamide " failure " (with a counterbalancing penicillin " success ") and three penicillin " failures " (with three counterbalancing sulphonamide " successes "). These cases have been specially shown in the Table and can be extracted if desired.

Although numerically small, the above group is of importance to the whole investigation. If restricted to comparisons of patients who recovered or died on only one method of treatment, it will be shown later that little difference was found between results of penicillin and sulphonamide treatments. The inclusion of " failures " altered the comparison appreciably and resulted in tables more in conformity with the clinical impression.

At the time when treatment schedules were drawn up, standard record forms were agreed for use in the inquiry. Acknowledgment is made of the valuable help given by Professors Mackie and Learmonth of the Departments of Bacteriology and Surgery of Edinburgh University in drafting these forms. As the record forms were extensive, they are not reproduced in this Report.

First Comments on Results

It is thought best, before giving the main comparisons involved in the inquiry, to comment on the results from the point of view of homogeneity of material, possible perturbing factors and re-classification. It may be stated here that the hospitals at which the agreed treatment was carried out were the City Hospital, Aberdeen ; the City Hospital, Edinburgh ; Belvidere and Ruchill Hospitals, Glasgow, and the County Hospital, Motherwell.

The *recoveries*, apart from one patient, do not demand detailed description at this stage ; but mention is necessary of this patient, a boy of one year admitted to hospital on the fourth day of his disease. He received penicillin for 5 days, pyrexia persisting for 4 days. The response to penicillin was most unsatisfactory and, 9 days after admission to hospital, he was put on sulphathiazole treatment (thereby becoming one of the " penicillin failures " to which reference has been already made). The response to sulphathiazole was good, though there was temporary paresis of muscles of the back and neck. The illness, it may be noted, was confirmed bacteriologically as meningococcal meningitis. By the twenty-seventh day of hospital treatment he was clinically and bacteriologically recovered and due for discharge in a day or two. At this stage he contracted Sonne dysentery, on recovery from which symptoms of meningeal irritation recurred. Further treatment by sulphonamide and penicillin failed to lead to improvement and the patient eventually died after 108 days' total residence in hospital. The last specimen of cerebro-spinal fluid obtained at lumbar puncture was examined by (*inter alia*) guinea-pig inoculation and this test for tuberculosis was positive. Permission was not granted for a post-mortem on the child. After consideration the case has been tabulated as a penicillin " failure " with subsequent sulphonamide " *success* " so far as treatment of the meningococcal meningitis is concerned.

The *deaths* will be discussed in their relation to known factors, when such factors are considered ; meantime, it may be noted that the twelve patients who died did survive for an average of 7·1 days after admission to hospital. If the practice had been followed of eliminating from the total cases those patients who died within 24 hours of admission, the total number of deaths would have been counted as six. Three patients survived 13, 19 and 30 days in hospital before dying. In the first of these, gastro-enteritis and congestion of the lungs had been found as complications during life ; post-mortem examination showed little evidence of any abnormal condition except congestion of the lungs ; histological examination of the lung tissue showed congestion of the alveolar capillaries ; the brain was normal and the comment was made that the patient had probably recovered from meningitis but died from another infection. In the second, blindness had been suspected as a complication during life ; there was no post-mortem examination. In the third, bronchitis and probably mild broncho-pneumonia, and hydrocephalus, had been found as complications during life ; post-mortem examination revealed that the brain substance was extremely soft and the pia-arachnoid over the base of the brain was opaque and swollen with gelatinised lymph ; the surface vessels were congested ; on section, the ventricle was found to be markedly dilated and the surrounding brain substance much thinned ; obstruction of the foramina of the fourth ventricle was not detected.

The *Age and Sex* distributions and the totals of the various treatments are given in Table 1. On examination of the original records, the age of some of the patients was too high to permit them to be included in the inquiry. The original age limitation to 0–4 inclusive was relaxed to 0–5 inclusive, so that all tables include children up to (but not of) six years of age. Of 86 patients for whom records were collected, 9 were eliminated because of too high age, leaving 31 patients on penicillin treatment only, 27 on sulphonamide treatment only, 4 (already mentioned) on successive treatments and 15 (to be mentioned later) on mixed treatment.

Inspection of the *age* distribution of the 62 patients in Table 1 reveals that the classification is too fine and that a summation into two main age groups would probably suffice, the dividing line being drawn at age 1. In fact it has been found, by a process of trial, that a division into patients under age 1 and aged 1–5 gives two age groups with more significant differences than any other dual division. Using this division, there were 32 treatments at age under 1 with 10 failures (including 9 deaths) and 34 treatments at ages 1–5 with 6 failures (including 3 deaths). The differences in failure and fatality rates, though not formally significant, are suggestive. In subsequent tables these age groups have been used.

The *sex* distribution gives 37 males and 25 females, the males being significantly in excess. Of the males, 9 died and, of the females, 3 ; taking treatments instead of cases, 12 out of 40 treatments in males failed, and 4 out of 26 in females. The fatality and failure rates do not differ significantly. It may therefore be legitimate to neglect sex, especially since the fatality and failure rates in patients of different sex in each of the two main age groups have not been found to differ significantly.

The recorded *complications* were as follows :—

(*a*) **Penicillin treatment only ;**

Age 2 months : Bronchitis, ? broncho-pneumonia and hydrocephalus. Died.
Age 3 months : ? Blindness. Died.
Age 6 months : Gastro-enteritis and pulmonary congestion. Died.
Age 7 months : Broncho-pneumonia. Died.
Age 1 year : Hydrocephalus. Recovered.

(*b*) **Sulphonamide treatment only ;**

Age 3 months : Pneumonia. Recovered.
Age 4 months : Lobar pneumonia. Died.
Age 6 months : Strabismus, facial paralysis, paralysis of muscles of back and neck. Recovered.
Age 2 years : Strabismus. Recovered.
Age 5 years : Herpes and Blepharitis. Recovered.

(*c*) **Successive treatments** (Penicillin followed by sulphonamide) ;

Age 7 months : Strabismus. (Penicillin failure, sulphonamide success).
Age 1 year : Paresis of muscles of back and neck, Sonne dysentery, tubercular meningitis (fatal, after recovery from acute infections). (Penicillin failure, sulphonamide success).
Age 3 years : Blindness. (Penicillin failure, sulphonamide success including recovery of vision).

Including all treatments in the above three groups, 8 failures (7 fatal) occurred in 50 treatments of patients without complications and 8 failures (5 fatal) occurred in 16 treatments of patients with complications. The difference between outcomes of uncomplicated and complicated cases being highly significant, the sub-division of cases according to the presence or absence of complications has been continued in later tables.

Such a finding also suggested the need to determine whether the less satisfactory results at age under 1 than at ages 1–5 are associated with a higher complication rate. Of 32 treatments of patients under 1, 9 were of patients with complications, and of 34 treatments of patients aged 1–5, 7 were of patients with complications. This slight excess of complications in the younger age group is easily attributable to chance.

The *duration of illness before admission* was commented on in the previous Report (Table VI) and found to have little apparent influence on the outcome, at least for durations up to 7 days. This, however, may not have applied to the present series and an examination has accordingly been made of Table 2. The mean duration for 58 cases in this series who received only one treatment was 4·57 days; for patients who recovered, the mean was 4·26 days and for those who died, the mean was 5·75 days—a difference which, though not statistically significant, is suggestive of a worsening of prognosis with delay in starting hospital treatment.

In the 58 patients who received only one treatment, those of age under 1 had a mean of 5·87 days' illness before admission, as against a mean of 3·18 days' illness in those aged 1–5. The difference is considerable and significant and, as it may have had an influence on the main results of the inquiry, further calculations have been made on the various smaller and less heterogeneous groups included in the inquiry, *e.g.*, on patients who did not have complications, etc. It is not proposed to give the results in full, but it may be stated that the only significant difference found was between the mean durations of illness on admission of (*a*) patients under the age of 1 and (*b*) patients aged 1–5, when the data were limited to patients who recovered. Complications were suggestively, but not significantly, associated with greater durations of illness before admission, both at all ages and in the two main age groups.

The *duration of primary pyrexia* in 46 patients who received only one treatment and recovered is shown in Table 3. The mean duration was 2·82 days. Patients under age 1 had a mean of 3·14 days, those aged 1–5 a mean of 2·54 days, a suggestive (but not significant) difference which supports the validity of distinguishing the two age groups. Similar comparisons limited to patients of the two age groups treated with the same product do not yield significant differences. Taking all patients who recovered (Table 3), those with complications had a less mean duration (2·1 days) than those without complications (mean 2·9 days). This surprising finding may be due to chance, but it can at least be deduced that the superimposing of complications on the original infection does not add to the length of the *primary* pyrexia.

The *duration of stay in hospital* of patients who recovered is given in Table 4. In forty-six patients receiving single treatments, the mean duration was 30·7 days. Comment has already been made on the duration of survival of certain patients who died. The mean duration for recoveries with single treatments, at age under 1, was 33·5 days and, at ages 1–5, 28·4 days; the difference is small and not significant. For the patients who received single treatments the mean duration of stay of those with complications (71 days) was very significantly greater than that of those without complications (25·1 days).

Correlations between measurable factors are of some interest. They may be summarised as follows:—

	Recoveries only, all treatments	
	r	P
Duration of illness before admission Duration of primary pyrexia	−0·0244	(large)
Duration of illness before admission Duration of stay in hospital	+0·3189	about ·01
Duration of primary pyrexia Duration of stay in hospital	+0·3615	under ·01

It is somewhat unexpected that association has not been found between the first two variables in the preceding table, though the result is perhaps consistent with the assessment made in the previous Report, that duration of illness before admission had little effect on fatality rate.

These findings, some of which have an interest quite apart from the main purpose of the present report, may be briefly summarized as follows :—It has been found that sex incidence though unequal, need not be separately entered ; that ages can best be grouped into those under 1 and those 1–5 ; that prognosis seems to worsen as the period of illness (before admission) lengthens and that patients aged less than 1 had a longer mean period than those aged 1–5 ; that the duration of primary pyrexia was rather longer in the younger age group ; that the occurrence of complications was a most (perhaps the most) important factor in determining the outcome, and in lengthening the period of hospital treatment of survivors ; and that the duration of illness before admission determines, to a considerable extent, the length of the period of stay in hospital of survivors, but not the duration of primary pyrexia.

Treatment Comparisons

Study of Tables 1–4 shows that treatments with penicillin numbered 35 with 11 unsuccessful results and treatments with sulphonamide numbered 31 with 5 unsuccessful results. In this comparison are included the four patients who had successive treatments. Although the difference does not attain formal significance penicillin seems to have been less efficacious than sulphonamide. (It has been calculated that with the limited clinical material available, any new method of treatment, *e.g.*, penicillin, would have had to eliminate deaths to show a significant improvement on the observed fatality rate under sulphonamide treatment. Alternatively, a quadrupling of the numbers in the inquiry would reveal the significance of the difference between the observed rates under penicillin treatment and sulphonamide treatment, if these rates were to remain static).

The lack of significant difference may have arisen because an inherent advantage of one method of treatment, *e.g.*, penicillin, had been overlaid by an excess of adverse factors in the group so treated. Such a possibility has been further investigated in the light of the findings of the preliminary section of this Report.

Although the *sex distribution* was not homogeneous, the lack of association of sex with other factors considered to affect outcome and already discussed above, makes us feel that this inequality does not vitiate the comparison.

Of more importance, however, the *age distribution* was not homogeneous The sulphonamide-treated group contained an excess of children aged less than 1 year. In the light of the preliminary discussions, such an excess would be expected to lead to a relatively high failure rate, although in fact the reverse was the case.

The *complications* have already been described and their importance noted. From the point of view of complications, the treatment groups were homogeneous—a weighty consideration in assessing their comparability.

The *duration of illness before admission* showed a minor difference between treatment groups. In view of the finding that, over all cases, this factor has affected the outcome in the present series, the comparability of the treatment groups in this respect is of some importance.

The *duration of primary pyrexia* did not show major differences between the treatment groups, taking only patients who recovered. If consideration is limited to patients who had no recorded complication and who recovered, there was still no major difference, though the mean duration in sulphonamide-treated patients (2·2 days) is suggestively lower than that of penicillin-treated patients (3·5 days).

The *duration of stay in hospital* has been already shown to be seriously affected by the presence of complications. Limiting consideration to patients without complications who recovered, the mean stay of penicillin-treated patients was 25 days, of sulphonamide-treated patients 21·4 days. The difference is small.

Brief consideration may now be given to those 15 patients who were given mixed treatment. Some of them had received deliberately on admission to hospital, dual treatment with penicillin and sulphonamide; others, who had started their hospital treatment as " penicillin only " cases, were found on later close enquiry to have had some sulphonamide before admission. The amount of sulphonamide so given was generally not large but it may have been sufficient to start bacteriostasis. The status of these last patients, compared with that of the four who received successive treatments, has been fully considered and the conclusion reached that it is proper to distinguish them as has been done in this Report.

In the " mixed treatment " group of 15, there was no death. Three males and one female were of age under 1, nine males and two females of ages 1–5. One patient aged 2 years had a complication (iridocyclitis) from which she recovered; no other complication was recorded. Numerical data for the groups were as follows :—

Mean duration of illness before admission, 3·6 days ;
Mean duration of primary pyrexia, 3·8 days ;
Mean duration of stay in hospital, 28 days.

The mixed treatment group, although comparable generally, had a *nil* mortality which differed suggestively from those of the specific treatment groups ; not only this, but there was a clinical impression that patients in this group made quite the most satisfactory progress.

Discussion

Although all patients treated with penicillin did not—as has already been mentioned—receive exactly the treatment laid down in the original schedule, it will be appreciated that variations would be found necessary in individual patients, according to the clinical assessments of severity and progress. However a sincere attempt was made to use the antibiotic according to the knowledge at present available regarding its administration.

It is clear that one of the results immediately apparent is the difficulty of assessing the value of a new method of treatment in meningococcal meningitis. In a comparatively small series, such as this, division into two groups reveals differences, both in homogeneity and in results of treatment, which do not emerge from the statistical analysis with the imprimatur of significance. Two of these differences, however, are worth emphasising. In the first place, of those who were given *penicillin*, 13 out of 31, or less than half, were under the age of 1 whereas of those who were given *sulphonamide* two-thirds of the patients (18 out of 27) were in this age group. Now according to our present knowledge of the behaviour of the disease such an inequality in age distribution should result in a worsening of the results in the sulphonamide group ; but in the event the 35 penicillin treatments showed 11 failures whereas the 31 sulphonamide treatments produced only 5. Such a result, converse to expectation, adds considerable weight to the impression gained clinically, as the trial progressed, that sulphonamides possessed a definite superiority over penicillin.

What weight should be attached to the results obtained in the group which received combined therapy, it is difficult to say. As it happened, this group contains the smallest proportion in the age group under 1, but the total number treated is too small to attach any great importance to the good results obtained. It was felt, however, to indicate a need to continue the investigation by comparing the effect of sulphonamide alone with that of sulphonamide and penicillin combined, and such a trial is now in progress.

One further finding may perhaps be mentioned. In our previous Report we recorded our inability to show a correlation between the duration of illness prior to admission and the ultimate outcome of treatment. In the present investigation too we are only able to record a suggestive statistical relationship ; but when the two age groups in the present enquiry are compared, one of the significant differences that emerges is the longer duration (5·9 days) of those under 1 compared with that (3·2 days) of those over 1. Although unable to produce satisfactory evidence that this is a factor in helping to produce the higher mortality in the young child, clinical prudence would suggest that early diagnosis with consequent early treatment is desirable. It is not sufficiently appreciated that even in non-epidemic times the first year of life contains an undue proportion of meningococcal infections. In this age period, therefore, earlier recourse to lumbar puncture as a diagnostic measure in cases presenting equivocal signs and symptoms should receive greater encouragement for it is only by a determined effort to attack the disease in this period of life that we can hope further to reduce mortality.

Summary

1. Of 62 patients under the age of 6 years, suffering from meningococcal meningitis, comparison has been made between 35 treatments with penicillin and 31 treatments with sulphonamides.

2. The inquiry was designed to secure treatment of alternate admissions with each product. Checking of results has shown that comparability was largely attained.

3. Sulphonamide alone gave suggestively better results (26 successful—84 per cent.) than penicillin alone (24 successful—69 per cent.). The numerical results are in accord with a strong clinical impression that sulphonamide alone was superior to penicillin alone, in the group studied.

4. Another group of 15 patients received mixed treatment and suffered no deaths. The experience of this group has determined the course of further inquiries which have been started.

Reference

(1) Department of Health for Scotland. *Sulphonamides in the Treatment of Meningococcal Meningitis.* (Report to the Scientific Advisory Committee). 1944.

TABLE 1

Treatments with Penicillin or Sulphonamide, by Sex, Age, Presence of Complications and Result

Completed Months of Age	PENICILLIN ONLY																SULPHONAMIDE ONLY																TOTAL TREATMENTS								Totals
	Males								Females								Males								Females								Both Sexes								
	C−				C+				C−				C+				C−				C+				C−				C+				C−				C+				
	R	D	S	F	R	D	S	F	R	D	S	F	R	D	S	F	R	D	S	F	R	D	S	F	R	D	S	F	R	D	S	F	R	D	S	F	R	D	S	F	
0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1
2	1	1	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	2	—	—	—	1	—	—	4
3	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—	—	2	—	—	—	1	1	—	—	4
4	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	3	—	—	—	—	—	—	—	1	—	—	—	—	1	—	—	6	—	—	—	—	1	—	—	7
5	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1	—	—	—	—	—	—	2
6	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—	—	1	1	—	—	3
7	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—	1	—	—	—	—	1	1	1	4
8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—	1
9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10 –	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—	2
11 –	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	3	—	—	—	—	—	—	—	3
12 –	3	—	1	—	—	—	—	1	3	—	—	—	1	—	—	—	—	1	—	1	—	—	1	—	2	—	—	—	—	—	—	—	8	1	1	1	1	—	1	1	14
24 –	4	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—	3	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	10	—	—	—	1	—	—	—	11
36 –	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	2	—	—	—	—	—	1	1	4
48–71	—	2	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—	—	2	2	—	—	1	—	—	—	5
0–71	15	3	1	—	—	4	—	2	7	1	—	—	1	—	—	1	9	2	—	1	1	—	2	—	10	1	—	—	3	1	1	—	41	7	1	1	5	5	3	3	66

C− : without complications. C+ : with complications. R : Recovery. D : Death.
S : successful treatment following a different (unsuccessful) treatment in the same patient.
F : failure of treatment (followed by a change of treatment).

As the above Table gives treatments and four patients had two treatments each, the total exceeds the total of patients by 4.

TABLE 2

Duration of Disease on Admission to Hospital

Each figure in brackets is the Duration for *one case*, in Days

Ages	Penicillin only				Sulphonamide only				Successive Treatments	
	C−		C+		C−		C+		C−	C+
	R	D	R	D	R	D	R	D	...	...
Under 1	(1) (1) (1) (2) (5) (6) (7)	(2) (9)	—	(1) (2) (4) (15)	(1) (2) (2) (2) (3) (3) (3) (3) (5) (8) (8) (28)	(0) (21)	(3) (27)	(1)	—	(14)
Total	23/7	11/2	—	22/4	68/12	21/2	30/2	1/1	—	14/1
1–5 ...	(1) (1) (2) (2) (2) (2) (3) (3) (3) (3) (4) (4) (5) (9) (10)	(1) (2)	(7)	—	(1) (1) (1) (2) (2) (2) (2)	(11)	(1) (2)	—	(3)	(3) (3)
Total	54/15	3/2	7/1	—	11/7	11/1	3/2	—	3/1	6/2

C− : without complications.
C+ : with complications.

R : Recovery.
D : Death.

TABLE 3

Duration of Primary Pyrexia (Recoveries only)

Each figure in brackets is the Duration for *one case*, in Days

Ages	Penicillin only		Sulphonamide only	
	C−	C+	C−	C+
Under 1 ...	(0) (2) (2) (5) (7) (9) (9)	—	(0) (0) (0) (0) (1) (1) (3) (3) (4) (4) (5) (6)	(0) (5)
Total ...	34/7 = 4·86d.	—	27/12 = 2·25d.	5/2
1–5 ...	(½) (1) (1) (1) (1) (2) (2) (2) (2) (3) (5) (5) (5) (5) (8)	(3)	(0) (0) (½) (1) (2) (2) (9)	(½) (2)
Total ...	43·5/15 = 2·9d.	3/1	14·5/7 = 2·07d.	2·5/2

C− : without complications. C+ : with complications.

TABLE 4

Duration of Stay in Hospital (*Recoveries only*)

Each figure in brackets is the duration for *one case*, in Days

Ages	Penicillin only		Sulphonamide only	
	C−	C+	C−	C+
Under 1	(21) (21) (23) (29) (31) (32) (35)	—	(10) (12) (21) (22) (24) (26) (26) (29) (31) (44) (48) (79)	(32) (108)
Total ...	192/7=27·4 days	—	372/12=31 days	140/2
1-5 ...	(10) (12) (13) (18) (22) (23) (23) (24) (25) (25) (26) (27) (29) (37) (45)	(164)	(10) (10) (13) (21) (26) (27) (28)	(25) (26)
Total ...	359/15=23·9 days	164/1	135/7=19·3 days	51/2

C− : without complications. C+ : with complications.

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